4-(1-Benzoylindol-3-yl)butyric Acids and FK143: Novel Nonsteroidal Inhibitors of Steroid 5α-Reductase (II)[1)]

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Received October 13, 1998; accepted December 24, 1998

A novel series of indolebutyric acids with varying benzoyl substituents were synthesized to develop nonsteroidal inhibitors of steroid 5α-reductase. We previously reported the discovery of a novel nonsteroidal 5α-reductase inhibitor, FR119680, which had an IC_{50} value of 5.0 nM against the rat prostatic enzyme. However, this compound was not strongly active against the human prostatic enzyme. By further study of the structure–activity relationships we succeeded in producing the strongly active compound, FK143, 4-[3-[3-[bis(4-isobutylphenyl)-methylamino]benzoyl]-1*H*-indol-1-yl]butyric acid, with an IC_{50} value of 1.9 nM against the human enzyme. FK143 also has *in vivo* inhibitory activity against the castrated young rat model and it should therefore be an extremely useful agent for the treatment of benign prostatic hyperplasia.

Key words 5α-reductase inhibitor; FK143; nonsteroidal; benign prostatic hyperplasia

Steroid 5α-reductase enzymatically converts testosterone (T) into 5α-dihydrotestosterone (DHT), which is the most active agonist for androgen receptors.[4)] An accumulation of DHT to high levels in the prostate gland or the skin is recognised as leading to various pathological conditions such as benign prostatic hyperplasia (BPH), acne, female hirsutism, and male pattern baldness.[5)] Therefore, therapy with a 5α-reductase inhibitor would be expected to lead to a decrease in DHT concentration within the prostate gland or other tissues, and may be an extremely useful agent for treatment of BPH and other diseases.

Though many laboratories have investigated 5α-reductase inhibitors,[6,7)] these efforts have predominantly concentrated on compounds with a steroidal structure, for example finasteride[6a)] (Table 3). However, due to the presence of a steroidal structure, there is the strong possibility of unwanted side-effects.[8)] We previously reported[1)] the discovery of an excellent nonsteroidal prototype compound, FR119680 (Fig. 1), which displays high *in vitro* inhibitory activity against rat prostatic 5α-reductase (IC_{50}=5.0 nM) and *in vivo* inhibitory activity against the castrated young rat model.[9)] However, further investigation of FR119680 revealed that it had only weak *in vitro* inhibitory activity against the human prostatic enzyme (IC_{50}=1.6 μM). Other derivatives based on the indole nucleus also did not have potent inhibitory activities against the human enzyme, thus, further modification was necessary.

A nonsteroidal inhibitor, ONO-3805, was reported in a patent by Nakai *et al.*[7b)] This compound displayed about three times stronger inhibitory activity against the human enzyme (IC_{50}=0.53 μM) than FR119080. The structures of FR119080 and ONO-3805 are quite different, however, there are some similarities in these two compounds. Both possess a carboxylic acid residue and a diaryl ether substituent at the same distance from the benzene ring of the corresponding nucleus. Therefore, we decided to introduce the same benzoyl substituent present in ONO-3805 to indole-3-butyric acid. The resulting compound **1** displayed stronger inhibitory activity against the human enzyme (IC_{50}=0.32 μM) than both FR119080 and ONO-3805. Thus, further modifications were then made to the *N*-benzoyl substituent of **1** to improve this activity further.

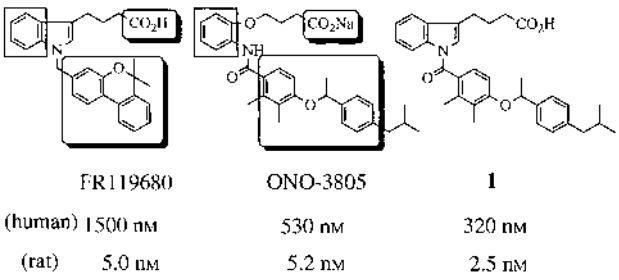

Fig. 1. Inhibition of Rat and Human Prostate 5α-Reductase by ONO-3805 and Indolebutyric Acids

Results and Discussion

Synthesis of Indole Derivatives Most *N*-benzoyl indole derivatives were synthesized by reaction of a phenyl ester of the benzoic acid and a dianion of indole-3-butyric acid, which was prepared from the corresponding carboxylic acid and sodium hydride in *N*,*N*-dimethylformamide (DMF) (Chart 1).

Modification of the *N*-Benzoyl Group The prepared compounds were evaluated for their ability to inhibit human prostatic 5α-reductase, and inhibitory activity was expressed as the IC_{50} value.

ONO-3805 was a racemic mixture due to the asymmetric center in the benzoyl substituent. Since racemic mixtures often cause trouble in development, we introduced achiral benzoyl substituents onto the indole nucleus. Several derivatives containing diaryl substituents were prepared from indole-3-butyric acid, examples of which are shown in Table 1 (**2**—**6**). Amongst them, the compound with a *m*-phenoxymethylbenzoyl substituent (**4**) had the strongest inhibitory activity: (IC_{50}=0.40 μM). Thus, further modifications were con-

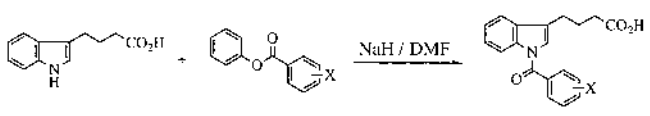

Chart 1

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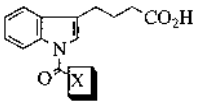
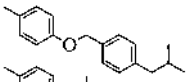
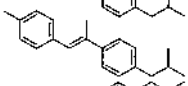
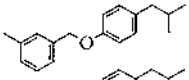
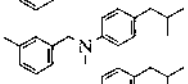
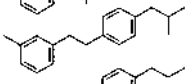
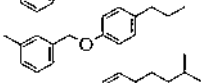
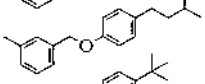
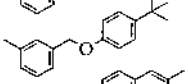
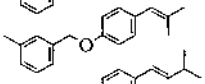
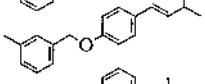
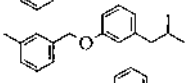
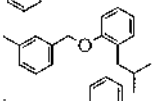
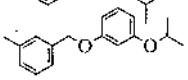
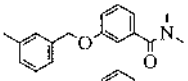
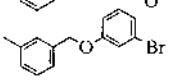
Table 1. Inhibition of Human Prostate 5α-Reductase by 4-(1-Benzoyl-1*H*-indol-3-yl)butyric Acids



Compd. No.	X	*In vitro* IC_{50} (nM) Human
2		1200
3		5600
4		400
5		860
6		850
7		2200
8		440
9		1800
10		880
11		810
12		78
13		230
14		300
15		8700
16		550

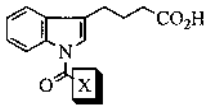
centrated on the terminal benzene ring of the benzoyl substituent of this compound.

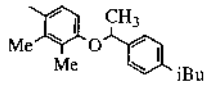
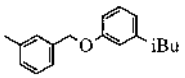
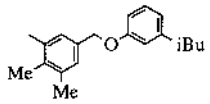
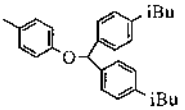
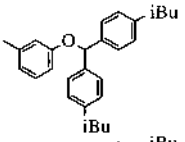
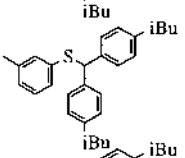
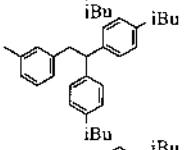
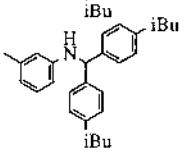
A variety of alkyl or alkenyl groups were introduced to the terminal benzene ring of the benzoyl substituent, examples of which are shown in Table 1 (**7**—**11**). Compounds with benzoyl groups bearing secondary alkyl groups; *e.g.* isobutyl and isopentyl (**4**, **8**), showed stronger activities than compounds with benzoyl groups bearing primary or tertiary alkyl groups; *e.g.* propyl, *tert*-butyl (**7**, **9**). Additionally, compounds bearing alkyl groups (**4**, **8**), were more active than compounds bearing alkenyl groups; *e.g.* isobutenyl, isopentenyl (**10**, **11**). As a result, the isobutyl group was selected as an optimum substituent.

Concerning the position of the substituent in the benzene ring, inspection of the data for *o*-, *m*-, and *p*-isobutyl (**13**, **12**, **4**) indicated clearly that the optimum position is *meta* and the compound with a *m*-isobutyl substituent (**12**) proved to have the highest activity (IC_{50}=78 nM) of the phenoxymethylbenzoyl derivatives.

Since a *m*-isobutyl substituent has strong activity, several

Table 2. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by 4-(1-Benzoyl-1*H*-indol-3-yl)butyric Acids



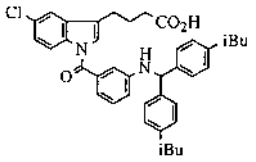
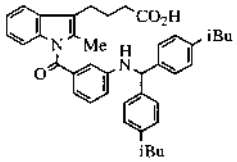
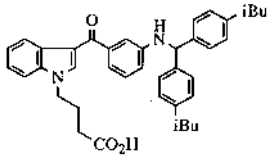
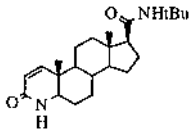
Compd. No.	X	*In vitro* IC_{50} (nM) Human	Rat	*In vivo* (*p.o.*)[a] 10 mg/kg (%)
1		320	2.5	33.8
12		65	1.7	6.9
17		89	2.7	−6.5
18		330	7.5	N.T.[b]
19		56	65	15.7
20		44	14	8.6
21		300	34	−2.3
22		38	75	44.1

a) *In vivo* effects of the indole compounds on ventral prostate weight of castrated rats (TP-treated). Prepubertal male rats were castrated, subcutaneously injected with 300 mg/kg of TP (except castrated control), and orally administered with drug suspension for 5 d. Data are expressed as percent reduction in prostate weight which was calculated as follows: 100[(prostate weight of test comp+TP group)−(prostate weight of castrated control group)]/[(prostate weight of vehicle+TP group)−(prostate weight of castrated control group)]. *b*) Not tested.

compounds containing other functional groups in the *meta*-position of the phenoxymethylbenzoyl substituent were prepared, examples of which are shown Table 1 (**14**, **15**, **16**). This table shows that the best substituent was an isobutyl group.

12 displayed strong *in vitro* inhibitory activity against not only the human prostatic enzyme, but also the rat prostatic enzyme (IC_{50}=1.7 nM). However, it did not display significant *in vivo* inhibitory activity in the castrated young rat model. In this model, the growth of ventral prostate is induced by subcutaneous injection of testosterone propionate (TP) to castrated young rats and is reduced by administration of the inhibitor.[9] ONO-3805 and **1** had strong *in vivo* in-

Table 3. Inhibition of Human and Rat Prostate 5α-Reductase and the Growth of Ventral Prostate in the Castrated Young Rat Model by **23**, **24**, FK143 and Finasteride

Compd. No.	Structure	*In vivo* IC_{50} (nM) Human	Rat	*In vivo* (*p.o.*)[a] 10 mg/kg (%)
23		>10000	49	N.T.[b]
24		1100	7.9	N.T.
FK143		1.9	4.2	46.1±2.2[c]
Finasteride		1.0	5.9	48.1±5.9[c]

a) *In vivo* effect of FK143 and finasteride on ventral prostate weight of castrated rats (TP-treated). See the footnotes of Table 2. *b*) Not tested. *c*) $p<0.01$ *vs.* Contol Dunnett *t*-test mean±S.E.

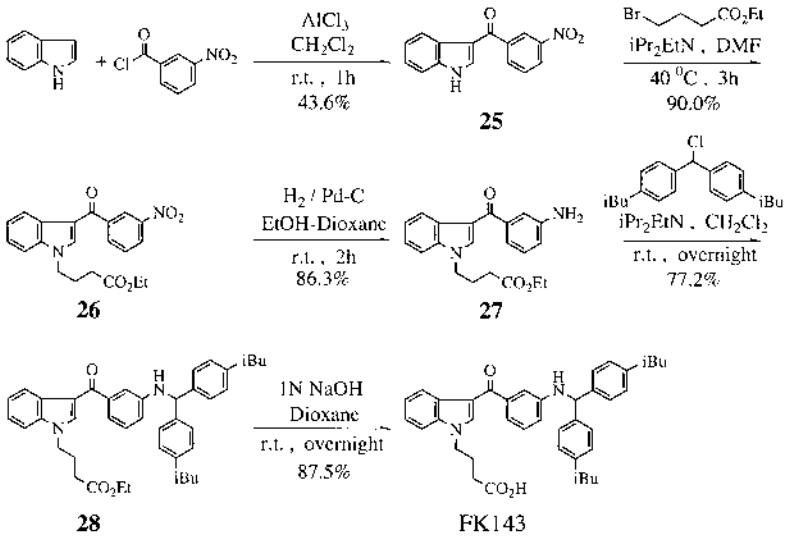


Chart 2

hibitory activity (Table 2). One of the differences in the structures of these compounds is the presence of methyl groups on the benzoyl substituent; that is **1** has two methyl groups in the benzoyl group and one methyl group on the carbon atom of the ether linker moiety. Thus, two methyl groups were introduced to the benzoyl group of **12**, however, the resulting compound **17** still displayed no significant *in vivo* inhibitory activity (Table 2).

Since the introduction of methyl groups to the benzene ring did not improve *in vivo* inhibitory activity, other modifications were examined. In order to avoid creation of an asymmetric center, a 4-isobutylphenyl group was introduced to the carbon atom of the ether bond instead of the methyl group; that is a bis(4-isobutylphenyl)methoxy group was introduced to the benzoyl group in the *para* and *meta* positions (**18**, **19**). The *meta* substituted compound **19** had strong *in vitro* inhibitory activity (IC_{50}=56 nM), however, it did not have any significant *in vivo* inhibitory activity.

Next we examined modification of the oxygen atom of the diphenylmethyloxy group of **19** by replacement with a sulfur

atom, CH_2 group and NH group (**20**—**22**). Amongst these compounds **22** had the strongest *in vitro* inhibitory activity (IC_{50}=38 nM), and also significant *in vivo* inhibitory activity at 10 mg/kg (*p.o.*).

22 displayed significant inhibitory activities both *in vitro* and *in vivo*, but did not show completely satisfactory *in vitro* inhibitory activity. In order to improve activity, further modifications were then examined. Several groups were introduced onto the indole nucleus of **22**; *e.g.* chloro (**23**) and methyl (**24**). However, these changes weakened human *in vitro* inhibitory activities. Interestingly, when we exchanged the positions of the two indole substituents of **22**, we obtained the best compound, FK143, which displayed ten times stronger *in vitro* inhibitory activity than **22**. FK143 had extremely strong inhibitory activity both *in vitro* and *in vivo*; its IC_{50} value was 1.9 nM against the human enzyme and it displayed strong *in vivo* inhibitory activity against the castrated young rat model at 10 mg/kg (*p.o.*).

Synthesis of FK143 FK143 was prepared as shown in Chart 2. The 3-benzoyl compound (**25**) was obtained by Friedel–Crafts reaction between indole and 3-nitrobenzoyl chloride; and *N*-alkylation of **25** was then achieved using ethyl 4-bromobutanoate and Hünig's base. The nitro group was converted to an amino group by catalytic hydrogenation and the diphenylmethyl was introduced to the amino group using bis(4-isobutylphenyl)methyl chloride and Hünig's base. The ester (**28**) was saponificated with 1 N sodium hydroxide to afford FK143.

Conclusions

We set out to produce 5α-reductase inhibitors with a nonsteroidal structure beginning with the indole nucleus of FR119080. By introducing a benzoyl substituent with a diphenylmethyl group and changing the positions of the substituents we have succeeded in producing the strongly active compound, FK143, which displays high *in vitro* inhibitory activity against human prostatic 5α-reductase[10] and, significantly, *in vivo* inhibitory activity against the castrated young rat model.[9] FK143 therefore has great potential to be an extremely useful agent for the treatment of BPH.

Experimental

Chemistry Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin Elmer 16PC fourier transform (FT) IR spectrometer. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker AM200 (200 MHz) spectrometer or a Varian Gemini-300 (300 MHz) spectrometer, and chemical shifts are reported in parts per million relative to tetramethyl silane (TMS) as internal standard (TMS, δ: 0.00). Mass spectra (MS) were obtained on a VG Platform.

4-[1-[2,3-Dimethyl-4-[1-(4-isobutylphenyl)ethoxy]benzoyl]-1*H*-indol-3-yl]butyric Acid (1) To a solution of 2,3-xylenol (19.45 g, 159 mmol) in CH_2Cl_2 (300 ml) was added a solution of bromine (8.20 ml, 159 mmol) in CH_2Cl_2 (20 ml) at −20 °C. After stirring at the same temperature for 1.5 h, the reaction mixture was washed with water and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (hexane) to give 4-bromo-2,3-xylenol (**1a**) (16.8 g, 52.5%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.37 (3H, s), 4.75 (1H, br s), 6.52 (1H, d, *J*=10 Hz), 7.42 (1H, d, *J*=10 Hz).

A mixture of **1a** (8.0 g, 40 mmol), 1-(4-isobutylphenyl)ethyl bromide (8.0 g, 33 mmol) and K_2CO_3 (11.58 g, 84 mmol) in DMF (130 ml) was stirred at 20 °C for 5.5 h. The reaction mixture was then poured into a mixture of water and EtOAc, and the organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) to give 4-bromo-2,3-dimethylphenyl 1-(4-isobutylphenyl)ethyl ether (**1b**) (9.77 g, 81.5%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, *J*=7 Hz), 1.62 (3H, d, *J*=7 Hz), 1.84 (1H, m), 2.29 (3H, s), 2.36 (3H, s), 2.44 (2H, d, *J*=7 Hz), 5.22 (1H, q, *J*=7 Hz), 6.45 (1H, d, *J*=10 Hz), 7.09 (2H, d, *J*=8 Hz), 7.17 (1H, d, *J*=10 Hz), 7.23 (2H, d, *J*=8 Hz).

A mixture of **1b** (3.66 g, 10 mmol), Mg (317 mg, 15 mmol) and 1,2-dibromoethane (0.1 ml) in tetrahydrofuran (THF) (40 ml) was stirred under reflux for 4 h. The reaction mixture was cooled to 20 °C and dry ice (2 g) was added. The reaction mixture was poured into a mixture of Et_2O and 1 N HCl, and the organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (hexane) to give 2,3-dimethyl-4-[1-(4-isobutylphenyl)ethoxy]benzoic acid (**1c**) (2.62 g, 79.3%) as a white solid, mp 139—140 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, *J*=7 Hz), 1.65 (3H, d, *J*=7 Hz), 1.84 (1H, m), 2.30 (3H, s), 2.45 (2H, d, *J*=7 Hz), 2.57 (3H, s), 5.37 (1H, q, *J*=7 Hz), 6.61 (1H, d, *J*=10 Hz), 7.10 (2H, d, *J*=8 Hz), 7.25 (2H, d, *J*=8 Hz), 7.75 (1H, d, *J*=10 Hz).

To a solution of DMF (0.79 g, 18.8 mmol) in CH_2Cl_2 (30 ml) was added $(COCl)_2$ (5 ml). After stirring at 20 °C for 2 h, the reaction mixture was concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (50 ml) and cooled to −45 °C, and a solution of **1c** (2.36 g, 7.2 mmol) in CH_2Cl_2 (20 ml) was added. After stirring at −45 °C for 2.5 h, the reaction mixture was added to a THF solution of sodium phenolate, which was prepared from NaH (60% dispersion in mineral oil; 1.44 g, 36 mmol) and phenol (3.39 g, 36 mmol) in THF (35 ml). After stirring at −45 °C for 30 min, the reaction mixture was poured into a mixture of 1 N HCl and EtOAc. The organic layer was separated, washed with water and brine and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) to give phenyl 2,3-dimethyl-4-[1-(4-isobutylphenyl)-ethoxy]benzoate (**1d**) (9.77 g, 90.4%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, *J*=7 Hz), 1.67 (3H, d, *J*=7 Hz), 1.84 (1H, m), 2.32 (3H, s), 2.44 (2H, d, *J*=7 Hz), 2.58 (3H, s), 5.38 (1H, q, *J*=7 Hz), 6.66 (1H, d, *J*=10 Hz), 7.00—7.20 (4H, m), 7.2—7.3 (3H, m), 7.3—7.5 (2H, m), 7.86 (1H, d, *J*=10 Hz).

Method A: A solution of 1*H*-indole-3-butyric acid (1.35 g, 6.65 mmol) in DMF (20 ml) was added to a suspension of NaH (60% dispersion in mineral oil; 0.80 g, 20 mmol) in DMF (30 ml) at −45 °C, and the reaction mixture was allowed to warm up to 0 °C. After stirring at 0 °C for 15 min, the reaction mixture was cooled to −20 °C, and a solution of **1d** (2.62 g, 6.52 mmol) in DMF (20 ml) was added. After stirring at −20 °C for 30 min, the reaction mixture was poured into chilled 1 N HCl. The mixture was extracted with EtOAc, and the extract washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (EtOAc–hexane) to give **1** (2.38 g, 71.5%) as colorless crystals, mp 98—99 °C. IR (KBr) cm^{-1}: 1720, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, *J*=7 Hz), 1.67 (3H, d, *J*=7 Hz), 1.85 (1H, m), 1.97 (2H, m), 2.22 (3H, s), 2.31 (3H, s), 2.32—2.50 (5H, m), 2.69 (2H, t, *J*=7 Hz), 5.36 (1H, q, *J*=7 Hz), 6.66 (1H, d, *J*=10 Hz), 6.86 (1H, s), 7.04 (1H, d, *J*=10 Hz), 7.11 (2H, d, *J*=8 Hz), 7.2—7.4 (4H, m), 7.5—7.6 (1H, m), 8.23 (1H, d, *J*=8 Hz). ESI-MS *m/z*: 510 $(M-H)^-$.

4-[1-[4-(4-Isobutylbenzyloxy)benzoyl]-1*H*-indol-3-yl]butyric Acid (2) A mixture of methyl 4-hydroxybenzoate (1.52 g, 10 mmol), 4-isobutylbenzyl chloride (2.0 g, 11 mmol) and K_2CO_3 (3.0 g, 22 mmol) in DMF (10 ml) was stirred at 50 °C for 6 h. The reaction mixture was poured into a mixture of 1 N HCl and EtOAc. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (hexane) to give methyl 4-(4-isobutylbenzyloxy)benzoate (**2a**) (1.98 g, 66.4%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, *J*=7 Hz), 1.7—2.1 (1H, m), 2.50 (2H, d, *J*=7 Hz), 3.87 (3H, s), 5.05 (2H, s), 7.00 (2H, d, *J*=10 Hz), 7.18 (2H, d, *J*=8 Hz), 7.33 (2H, d, *J*=8 Hz), 8.00 (2H, d, *J*=10 Hz).

To a solution of **2a** (1.9 g, 6.4 mmol) in 1,4-dioxane (10 ml) was added 1 N NaOH (10 ml, 10 mmol), and the mixture was stirred at 20 °C for 3 h. After acidification with 1 N HCl, the mixture was extracted with EtOAc. The extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (hexane) to give 4-(4-isobutylbenzyloxy)benzoic acid (**2b**) (1.78 g, 98.3%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, *J*=7 Hz), 1.7—2.0 (1H, m), 2.50 (2H, d, *J*=7 Hz), 5.08 (2H, s), 7.02 (2H, d, *J*=10 Hz), 7.18 (2H, d, *J*=8 Hz), 7.35 (2H, d, *J*=8 Hz), 8.06 (2H, d, *J*=10 Hz).

To a solution of **2b** (1.71 g, 6.0 mmol) in CH_2Cl_2 (30 ml) were added $(COCl)_2$ (0.6 ml, 6.8 mmol) and DMF (0.05 ml). After stirring at 20 °C for 2 h, the mixture was concentrated *in vacuo*. The residue was dissolved in THF (15 ml) and the solution was added to a solution of sodium phenolate, prepared from NaH (60% dispersion in mineral oil; 0.72 g, 18 mmol) and phenol (1.69 g, 18 mmol) in THF (17 ml). After stirring at 20 °C for 15 min,

the mixture was poured into a mixture of 1 N HCl and EtOAc. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized (diisopropyl ether (IPE)) to give phenyl 4-(4-isobutylbenzyloxy)benzoate (**2c**) (1.83 g, 84.7%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.7—2.0 (1H, m), 2.50 (2H, d, J=7 Hz), 5.10 (2H, s), 7.05 (2H, d, J=10 Hz), 7.1—7.5 (9H, m), 8.17 (2H, d, J=10 Hz).

Following method A, **2** (1.18 g, 60.5%) was prepared from 1*H*-indole-3-butyric acid (1.0 g) and **2c** (1.50 g) as a colorless solid, mp 156—157 °C. IR (KBr) cm^{-1}: 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=7 Hz), 1.8—2.2 (3H, m), 2.4—2.6 (4H, m), 2.78 (2H, t, J=7 Hz), 5.15 (2H, s), 7.12 (2H, d, J=10 Hz), 7.2—7.5 (7H, m), 7.6 (1H, m), 7.75 (2H, d, J=10 Hz) , 8.35 (1H, m). ESI-MS *m*/*z*: 468 (M−H)$^-$.

4-[1-[4-[2-(4-Isobutylphenyl)-1-propenyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (3) To a solution of 1-(4-isobutylphenyl)ethyltriphenylphosphonium bromide (12.7 g) in THF (120 ml) was added a solution of *tert*-BuOK (12.7 g) in THF (80 ml) at 20 °C over 45 min. The reaction mixture was then stirred at 25 °C for 1 h, and a solution of methyl 4-formylbenzoate (1.93 g) in THF (20 ml) was added. After stirring for 10 h, the reaction mixture was poured into a mixture of EtOAc and 1 N HCl. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 20) to give methyl 4-[2-(4-isobutylphenyl)-1-propenyl]-benzoate (**3a**) (1.69 g, 43.2%) as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.7—2.1 (1H, m), 2.30 (3H, s), 2.50 (2H, d, J=7 Hz), 3.90 (3H, s), 6.82 (1H, s), 7.15 (2H, d, J=8 Hz), 7.40 (2H, d, J=8 Hz), 7.45 (2H, d, J=10 Hz), 8.05 (2H, d, J=10 Hz).

Following the procedure described above for **2b**, **3a** (1.49 g) was hydrolyzed with 1 N NaOH to give 4-[2-(4-isobutylphenyl)-1-propenyl]benzoic acid (**3b**) (1.01 g, 71.3%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.7—2.1 (1H, m), 2.30 (3H, s), 2.50 (2H, d, J=7 Hz), 6.85 (1H, s), 7.18 (2H, d, J=10 Hz), 7.45 (4H, d, J=10 Hz), 8.05 (2H, d, J=10 Hz).

Following the procedure described above for **2c**, phenyl 4-[2-(4-isobutylphenyl)-1-propenyl]benzoate (**2c**) (402 mg, 63.9%) was prepared from **3b** (500 mg) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.7—2.1 (1H, m), 2.30 (3H, s), 2.50 (2H, d, J=7 Hz), 6.90 (1H, s), 7.15—7.35 (5H, m), 7.40—7.55 (6H, m), 8.20 (2H, d, J=10 Hz).

Following method A, **3** (370 mg, 72.9%) was prepared from 1*H*-indole-3-butyric acid (237 mg) and **3c** (393 mg) as colorless crystals. IR (KBr) cm^{-1}: 1720, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=7 Hz), 1.78—1.96 (1H, m), 2.04 (2H, quintet, J=7 Hz), 2.34 (3H, s), 2.45 (2H, t, J=7 Hz), 2.50 (2H, d, J=7 Hz), 2.78 (2H, t, J=7 Hz), 6.86 (1H, s), 7.16 (1H, s), 7.18 (2H, d, J=10 Hz), 7.28—7.43 (2H, m), 7.46 (2H, d, J=10 Hz), 7.50 (2H, d, J=10 Hz), 7.58 (1H, dd, J=1, 8 Hz), 7.74 (2H, d, J=10 Hz), 8.38 (1H, dd, J=1, 8 Hz). ESI-MS *m*/*z*: 478 (M−H)$^-$.

4-[1-[3-(4-Isobutylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (4) A mixture of 4-isobutylphenol (1.0 g, 6.66 mmol), methyl 3-(bromomethyl)benzoate (1.52 g, 6.66 mmol) and K_2CO_3 (1.84 g, 13.2 mmol) in DMF (20 ml) was stirred at 20 °C overnight. The reaction mixture was partitioned between Et_2O and 1 N HCl, and the organic layer washed with water and brine then dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give methyl 3-(4-isobutylphenoxymethyl)benzoate (**4a**) (1.75 g, 88.1%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.41 (2H, d, J=7 Hz), 3.92 (3H, s), 5.08 (2H, s), 6.90 (2H, d, J=10 Hz), 7.08 (2H, d, J=10 Hz), 7.46 (1H, t, J=8 Hz), 7.66 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.12 (1H, t, J=1 Hz).

Following the procedure described above for **2b**, **4a** (1.6 g) was hydrolyzed with 1 N NaOH to give 3-(4-isobutylphenoxymethyl)benzoic acid (**4b**) (1.25 g, 82%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.42 (2H, d, J=7 Hz), 5.10 (2H, s), 6.90 (2H, d, J=10 Hz), 7.06 (2H, d, J=10 Hz), 7.50 (1H, t, J=8 Hz), 7.72 (1H, dd, J=1, 8 Hz), 8.08 (1H, dd, J=1, 8 Hz), 8.18 (1H, t, J=1 Hz).

Following the procedure described above for **2c**, phenyl 3-(4-isobutylphenoxymethyl)benzoate (**4c**) (1.52 g, 99.9%) was prepared from **4b** (1.20 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.42 (2H, d, J=7 Hz), 5.12 (2H, s), 6.90 (2H, d, J=10 Hz), 7.08 (2H, d, J=10 Hz), 7.18—7.50 (5H, m), 7.53 (1H, t, J=8 Hz), 7.74 (1H, dd, J=1, 8 Hz), 8.18 (1H, dd, J=1, 8 Hz), 8.28 (1H, t, J=1 Hz).

Following method A, **4** (1.45 g, 74.2%) was prepared from 1*H*-indole-3-butyric acid (846 mg) and **4c** (1.50 g) as colorless crystals, mp 114—115 °C. IR (KBr) cm^{-1}: 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7 Hz), 1.70—1.92 (1H, m), 2.02 (2H, quintet, J=7 Hz), 2.36—2.50 (4H, m), 2.75 (2H, t, J=7 Hz), 5.12 (2H, s), 6.88 (2H, d, J=8 Hz), 7.07 (2H, d, J=8 Hz), 7.08 (1H, s), 7.25—7.40 (2H, m), 7.48—7.60 (2H, m), 7.65 (1H, s), 7.68 (1H, d, J=8 Hz), 7.80 (1H, t, J=1 Hz), 8.38 (1H, dd, J=1, 8 Hz). ESI-MS *m*/*z*: 468 (M−H)$^-$.

4-[1-[3-[*N*-(4-Isobutylphenyl)-*N*-methylaminomethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (5) A mixture of 4-isobutyl-*N*-methylaniline (1.3 g, 7.96 mmol), methyl 3-bromomethylbenzoate (2.01 g, 8.76 mmol) and iPr_2NEt (2.77 ml, 15.9 mmol) in CH_2Cl_2 (20 ml) was stirred at 20 °C for 3 h. The reaction mixture was then partitioned betweeen EtOAc and water, and the organic layer washed with water and brine, and dried over $MgSO_4$. Evaporation of solvent gave crude methyl 3-[*N*-(4-isobutylphenyl)-*N*-methylaminomethyl]benzoate (**5a**) (2.70 g) as a pale yellow oil, which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.80 (1H, m), 2.37 (2H, d, J=7 Hz), 2.98 (3H, s), 3.90 (3H, s), 4.52 (2H, s), 6.68 (2H, d, J=10 Hz), 7.00 (2H, d, J=10 Hz), 7.38 (1H, t, J=8 Hz), 7.45 (1H, dd, J=1, 8 Hz), 7.92 (1H, dd, J=1, 8 Hz), 7.95 (1H, t, J=1 Hz).

To a solution of crude **5a** (2.6 g) in THF (30 ml) were added 1 N NaOH (16.7 ml) and MeOH (15 ml). The reaction mixture was stirred at 20 °C for 4 h and organic solvent removed by evaporation. The aqueous layer was then acidified with 1 N HCl and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$ and evaporated. The residue was then triturated with EtOAc to give 3-[*N*-(4-isobutylphenyl)-*N*-methylaminomethyl]benzoic acid (**5b**) (1.20 g, 48.3%) as a white solid. ^{1}H-NMR (DMSO-d_6) δ: 0.82 (6H, d, J=7 Hz), 1.74 (1H, m), 2.30 (2H, d, J=7 Hz), 2.96 (3H, s), 4.56 (2H, s), 6.64 (2H, d, J=10 Hz), 6.93 (2H, d, J=10 Hz), 7.34—7.45 (2H, m), 7.82 (2H, br s).

Following the procedure described above for **2c**, phenyl 3-[*N*-(4-isobutylphenyl)-*N*-methylaminomethyl]benzoate (**5c**) (300 mg, 68.3%) was prepared from **5b** (350 mg) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.80 (1H, m), 2.37 (2H, d, J=7 Hz), 2.98 (3H, s), 3.90 (3H, s), 4.52 (2H, s), 6.68 (2H, d, J=10 Hz), 7.00 (2H, d, J=10 Hz), 7.38 (1H, t, J=8 Hz), 7.45 (1H, dd, J=1, 8 Hz), 7.92 (1H, dd, J=1, 8 Hz), 7.95 (1H, t, J=1 Hz).

Following method A, **5** (83 mg, 22.1%) was prepared from 1*H*-indole-3-butyric acid (189 mg) and **5c** (290 mg) as colorless crystals, mp 78—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.78 (1H, m), 1.98 (2H, quintet, J=7 Hz), 2.36 (2H, d, J=7 Hz), 2.40 (2H, t, J=7 Hz), 2.70 (2H, t, J=7 Hz), 3.00 (3H, s), 4.53 (2H, s), 6.70 (2H, d, J=10 Hz), 6.98 (2H, d, J=10 Hz), 7.04 (1H, s), 7.32 (1H, t, J=8 Hz), 7.38 (1H, t, J=8 Hz), 7.46 (1H, d, J=8 Hz), 7.48 (1H, s), 7.55 (1H, d, J=8 Hz), 7.58—7.64 (2H, m), 8.37 (1H, d, J=8 Hz). ESI-MS *m*/*z*: 481 (M−H)$^-$.

4-[1-[3-[2-(4-Isobutylphenyl)ethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (6) Following the procedure described above for **3b**, (*E*)-3-cyano-4′-isobutylstilbene (**6a**) (995 mg, 43.3%) was prepared from 4-isobutylbenzyltriphenylphosphonium chloride (4.7 g) and 3-cyanobenzaldehyde (1.15 g). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.50 (2H, d, J=7 Hz), 7.00 (1H, d, J=17 Hz), 7.14 (1H, d, J=17 Hz), 7.16 (1H, d, J=8 Hz), 7.40—7.55 (4H, m), 7.70 (1H, m), 7.75 (1H, m).

A solution of **6a** (875 mg, 3.35 mmol) in a mixture of 3 N HCl (15 ml) and formic acid (50 ml) was heated under reflux with stirring for 3 d. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The extract was washed with water and brine and dried over $MgSO_4$. After evaporation of solvent, the residue was recrystallized (IPE) to give (*E*)-4′-isobutylstilbene-3-carboxylic acid (**6b**) (512 mg, 54.5%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.49 (2H, d, J=7 Hz), 7.05—7.25 (4H, m), 7.39—7.50 (3H, m), 7.70 (1H, m), 7.95 (1H, m), 8.22 (1H, m).

Following the procedure described above for **2c**, phenyl (*E*)-4′-isobutylstilbene-3-carboxylate (**6c**) (419 mg, 79.2%) was prepared from **5b** (416 mg). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J=7 Hz), 1.92 (1H, m), 2.52 (2H, d, J=7 Hz), 7.10—7.40 (5H, m), 7.40—7.60 (5H, m), 7.78 (1H, m), 8.10 (1H, m), 8.38 (1H, m).

Following method A, (*E*)-4-[1-[3-[2-(4-isobutylphenyl)ethenyl]benzoyl]-1*H*-indol-3-yl]butyric acid (**6d**) (260 mg, 46.8%) was obtained from 1*H*-indole-3-butyric acid (250 mg) and **6c** (1.50 g). NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.88 (1H, m), 2.01 (2H, m), 2.35—2.50 (4H, m), 2.75 (2H, t, J=7 Hz), 7.0—7.6 (12H, m), 7.77 (1H, m), 7.87 (1H, m), 8.40 (1H, m).

A solution of **6d** (150 mg, 0.322 mmol) in MeOH (20 ml) was hydrogenated over 10% Pd–C (100 mg) under H_2 (1.5 atm) at 20 °C for 3 h. After removal of catalyst, the solvent was evaporated. The residue was purified by preparative thin layer chromatography (PTLC) (silica gel, 5% MeOH in $CHCl_3$) to give **6** (98 mg, 65.1%), mp 110—111 °C. IR (KBr) cm^{-1}: 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.72—1.92 (1H, m), 2.02

(2H, quintet, J=7 Hz), 2.42 (2H, d, J=7 Hz), 2.44 (2H, t, J=7 Hz), 2.76 (2H, t, J=7 Hz), 2.86—3.06 (4H, m), 7.00—7.15 (5H, m), 7.30— 7.45 (4H, m), 7.45— 7.60 (3H, m), 8.35 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 466 $(M-H)^-$.

4-[1-[3-(4-Propylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (7) Following the procedure described above for **4a**, methyl 3-(4-propylphenoxymethyl)benzoate (**7a**) (2.51 g, 100%) was prepared from 4-propylphenol (1.31 g) and methyl 3-(bromomethyl)benzoate (2.0 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, t, J=7 Hz), 1.62 (1H, sextet, J=7 Hz), 2.55 (2H, t, J=7 Hz), 3.94 (3H, s), 5.08 (2H, s), 6.89 (2H, d, J=8 Hz), 7.10 (2H, d, J=8 Hz), 7.46 (1H, t, J=8 Hz), 7.66 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.12 (1H, t, J=1 Hz).

Following the procedure described above for **5b**, **7a** (2.5 g) was hydrolyzed with 1 N NaOH to give 3-(4-propylphenoxymethyl)benzoic acid (**7b**) (2.0 g, 88.4%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7 Hz), 1.61 (1H, sextet, J=7 Hz), 2.55 (2H, d, J=7 Hz), 5.10 (2H, s), 6.92 (2H, d, J=8 Hz), 7.12 (2H, d, J=8 Hz), 7.51 (1H, t, J=8 Hz), 7.72 (1H, d, J=8 Hz), 8.10 (1H, d, J=8 Hz), 8.18 (1H, s).

Following the procedure described above for **2c**, phenyl 3-(4-propylphenoxymethyl)benzoate (**7c**) (2.1 g, 91.0%) was prepared from **7b** (1.8 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7 Hz), 1.51 (2H, sextet, J=7 Hz), 2.54 (2H, t, J=7 Hz), 5.12 (2H, s), 6.92 (2H, d, J=8 Hz), 7.12 (2H, d, J=8 Hz), 7.18—7.48 (5H, m), 7.54 (1H, t, J=8 Hz), 7.72 (1H, dd, J=1, 8 Hz), 8.17 (1H, dd, J=1, 8 Hz), 8.27 (1H, t, J=1 Hz).

Following method A, **7** (1.70 g, 62.2%) was prepared from 1*H*-indole-3-butyric acid (1.22 g) and **7c** (2.08 g) as colorless crystals, mp 102—103 °C. IR (KBr) cm^{-1}: 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7 Hz), 1.64 (2H, sextet, J=7 Hz), 2.07 (2H, quintet, J=7 Hz), 2.46 (2H, t, J=7 Hz), 2.57 (2H, t, J=7 Hz), 2.78 (2H, t, J=7 Hz), 5.16 (2H, s), 6.94 (2H, t, J=8 Hz), 7.11 (1H, s), 7.14 (2H, t, J=8 Hz), 7.32—7.46 (2H, m), 7.53—7.62 (2H, m), 7.71 (2H, d, J=8 Hz), 7.82 (1H, d, J=1 Hz), 8.42 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 454 $(M-H)^-$.

4-[1-[3-(4-Isopentylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (8) Following the procedure described above for **3a**, methyl (*E*)-3-[4-(3-methyl-1-butenyl)phenoxymethyl]benzoate (**8a**) (3.44 g, 99.8%) was prepared from isobutyltriphenylphosphonium bromide (6.65 g) and methyl 3-(4-formylphenoxymethyl)benzoate (3.0 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d, J=7 Hz), 2.89 (1H, m), 3.98 (3H, s), 5.11 (2H, s), 5.39 (2H, dd, J=7, 10 Hz), 6.23 (1H, d, J=10 Hz), 6.83 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.47 (1H, t, J=8 Hz), 7.66 (2H, dd, J=1, 8 Hz), 8.03 (2H, dd, J=1, 8 Hz), 8.13 (1H, t, J=1 Hz).

8a (1.85 g, 5.96 mmol) was hydrogenated over 10% Pd–C (185 mg) under H_2 (4 atm) to give methyl 3-(4-isopentylphenoxymethyl)benzoate (**8b**) (1.85 g, 99.4%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.40—1.70 (3H, m), 2.56 (2H, dd, J=7, 8 Hz), 3.92 (3H, s), 5.08 (2H, s), 6.88 (2H, d, J=8 Hz), 7.08 (2H, d, J=8 Hz), 7.46 (1H, t, J=8 Hz), 7.65 (2H, dd, J=1, 8 Hz), 8.00 (2H, dd, J=1, 8 Hz), 8.12 (1H, t, J=1 Hz).

Following the procedure described above for **5b**, **8b** (1.84 g) was hydrolyzed with 1 N NaOH (8.83 ml) to give 3-(4-isopentylphenoxymethyl)-benzoic acid (**8c**) (1.55 g, 88.2%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=7 Hz), 1.40—1.70 (3H, m), 2.57 (2H, dd, J=7, 8 Hz), 5.12 (2H, s), 6.90 (2H, d, J=8 Hz), 7.12 (2H, d, J=8 Hz), 7.51 (1H, t, J=8 Hz), 7.72 (2H, dd, J=1, 8 Hz), 8.08 (2H, dd, J=1, 8 Hz), 8.19 (1H, t, J=1 Hz).

Following the procedure described above for **2c**, phenyl 3-(4-isopentylphenoxymethyl)benzoate (**8d**) (1.85 g, 98.2%) was obtained from **8c** (1.5 g). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.40—1.70 (3H, m), 2.57 (2H, dd, J=7, 8 Hz), 5.12 (2H, s), 6.92 (2H, dd, J=8 Hz), 7.12 (2H, d, J=8 Hz), 7.20—7.60 (6H, m), 7.73 (2H, dd, J=1, 8 Hz), 8.18 (2H, dd, J=1, 8 Hz), 8.29 (1H, t, J=1 Hz).

Following method A, **8** (1.90 g, 80.0%) was obtained from 1*H*-indole-3-butyric acid (1.0 g) and **8d** (1.84 g), mp 115—116 °C. IR (KBr) cm^{-1}: 1715, 1675. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (6H, d, J=7 Hz), 1.40—1.70 (3H, m), 2.01 (2H, quintet, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.54 (2H, dd, J=7, 8 Hz), 2.72 (2H, t, J=7 Hz), 5.10 (2H, s), 6.90 (2H, d, J=8 Hz), 7.08 (1H, s), 7.12 (2H, d, J=8 Hz), 7.26—7.38 (2H, m), 7.47—7.54 (2H, m), 7.67 (2H, dd, J=1, 8 Hz), 7.78 (1H, t, J=1 Hz), 8.37 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 482 $(M-H)^-$.

4-[1-[3-(4-*tert*-Butylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (9) Following the procedure described above for **4a**, methyl 3-(4-*tert*-butylphenoxymethyl)benzoate (**9a**) (3.23 g, 108.2%) was obtained from 4-*tert*-butylphenol (1.5 g) and methyl 3-(bromomethyl)benzoate (2.29 g) as an oil, which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (9H, s), 3.94 (3H, s), 5.10 (2H, s), 6.92 (2H, d, J=8 Hz), 7.32 (2H, d, J=8 Hz), 7.47 (1H, t, J=8 Hz), 7.66 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.26 (1H, t, J=1 Hz).

Following the procedure described above for **5b**, **9a** (3.23 g) was hydrolyzed with 1 N NaOH to give 3-(4-*tert*-butylphenoxymethyl)benzoic acid (**9b**) (2.52 g, 82.1%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (9H, s), 5.12 (2H, s), 6.93 (2H, d, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.52 (1H, t, J=8 Hz), 7.72 (1H, d, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.20 (1H, s).

Following the procedure described above for **2c**, phenyl 3-(4-*tert*-butylphenoxymethyl)benzoate (**9c**) (3.16 g, 99.7%) was prepared from **9b** (2.50 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (9H, s), 5.13 (2H, s), 6.94 (2H, d, J=8 Hz), 7.20—7.55 (7H, m), 7.55 (1H, t, J=8 Hz), 7.74 (1H, dd, J=1, 8 Hz), 8.16 (1H, dd, J=1, 8 Hz), 8.27 (1H, t, J=1 Hz).

Following method A, **9** (3.50 g, 86.5%) was prepared from 1*H*-indole-3-butyric acid (1.78 g) and **8c** (3.10 g) as colorless crystals, mp 125—127 °C. IR (KBr) cm^{-1}: 1700, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (9H, s), 2.02 (2H, quintet, J=7 Hz), 2.43 (2H, t, J=7 Hz), 2.74 (2H, t, J=7 Hz), 5.13 (2H, s), 6.92 (2H, d, J=8 Hz), 7.06 (1H, s), 7.28—7.42 (4H, m), 7.50—7.58 (2H, m), 7.65 (2H, d, J=8 Hz), 7.78 (1H, d, J=1 Hz), 8.37 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 468 $(M-H)^-$.

4-[1-[3-[4-(2-Methyl-2-propenyl)phenoxymethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (10) A 1.6 M solution of BuLi in hexane (6.9 ml, 11.1 mmol) was added to a suspension of isopropyltriphenylphosphonium iodide (4.8 g, 11.1 mmol) in THF (100 ml) at 0 °C, and the mixture was stirred at 20 °C for 2 h. The reaction mixture was cooled to 0 °C and a solution of methyl 3-(4-formylphenoxymethyl)benzoate (2.0 g, 7.40 mmol) in THF (10 ml) was added. After stirring at 0 °C for 1 h, the reaction mixture was partitioned between ether and 1 N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 5) to give methyl 3-[4-(2-methyl-2-propenyl)phenoxymethyl]benzoate (**10a**) (1.02 g, 46.5%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (3H, d, J=1 Hz), 1.88 (3H, d, J=1 Hz), 3.94 (1H, s), 5.10 (2H, s), 6.20 (1H, br s), 6.92 (2H, d, J=9 Hz), 7.16 (2H, d, J=9 Hz), 7.46 (1H, t, J=8 Hz), 7.65 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.12 (1H, t, J=1 Hz).

Following the procedure described above for **5b**, **10a** (0.98 g) was hydrolyzed with 1 N NaOH to give 3-[4-(2-methyl-2-propenyl)phenoxymethyl]-benzoic acid (**10b**) (0.83 g, 88.8%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, d, J=1 Hz), 1.88 (3H, d, J=1 Hz), 5.12 (2H, s), 6.20 (1H, br s), 6.94 (2H, d, J=8 Hz), 7.17 (2H, d, J=8 Hz), 7.51 (1H, t, J=7 Hz), 7.77 (1H, d, J=7 Hz), 8.00 (1H, d, J=7 Hz), 8.12 (1H, s).

Following the procedure described above for **2c**, phenyl 3-[4-(2-methyl-2-propenyl)phenoxymethyl]benzoate (**10c**) (1.05 g, 84.2%) was prepared from **10b** (0.98 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, d, J=1 Hz), 1.88 (3H, d, J=1 Hz), 5.14 (2H, s), 6.20 (1H, bs), 6.94 (2H, d, J=8 Hz), 7.15—7.32 (4H, m), 7.56 (1H, d, J=8 Hz), 7.75 (1H, d, J=8 Hz), 8.18 (1H, d, J=8 Hz), 8.30 (1H, s).

Following method A, **10** (0.80 g, 61.3%) was prepared from 1*H*-indole-3-butyric acid (576 mg) and **10c** (1.0 g) as colorless crystals, mp 102—103 °C. IR (KBr) cm^{-1}: 1715, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, d, J=1 Hz), 1.88 (3H, d, J=1 Hz), 2.02 (2H, quintet, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.74 (2H, t, J=7 Hz), 5.16 (2H, s), 6.20 (1H, br s), 6.92 (2H, d, J=8 Hz), 7.05 (1H, s), 7.16 (2H, d, J=8 Hz), 7.28—7.44 (2H, m), 7.51—7.71 (4H, m), 7.82 (1H, s), 8.38 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 466 $(M-H)^-$.

(*E*)-4-[1-[3-[4-(3-Methyl-2-butenyl)phenoxymethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (11) Following the procedure described above for **5b**, methyl (*E*)-3-[4-(3-methyl-1-butenyl)phenoxymethyl]benzoate (**8a**) (1.50 g) was hydrolyzed with 1 N NaOH to give (*E*)-3-[4-(3-methyl-1-butenyl)phenoxymethyl]benzoic acid (**11a**) (1.33 g, 92.9%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, J=7 Hz), 2.82—3.00 (1H, m), 5.13 (2H, s), 5.41 (1H, dd, J=10, 11 Hz), 6.24 (1H, d, J=11 Hz), 6.95 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.52 (1H, t, J=7 Hz), 7.72 (1H, d, J=7 Hz), 8.08 (1H, d, J=7 Hz), 8.18 (1H, s).

Following the procedure described above for **2c**, phenyl (*E*)-3-[4-(3-methyl-1-butenyl)phenoxymethyl]benzoate (**11b**) (1.50 g, 91.7%) was prepared from **11a** (1.30 g). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, d, J=7 Hz), 2.82—3.00 (1H, m), 5.14 (2H, s), 5.39 (1H, dd, J=10, 11 Hz), 6.22 (1H, d, J=11 Hz), 6.95 (2H, d, J=8 Hz), 7.18—7.58 (8H, m), 7.73 (1H, d, J=7 Hz), 8.16 (1H, d, J=7 Hz), 8.26 (1H, s).

Following method A, **11** (1.50 g, 66.7%) was prepared from 1*H*-indole-3-butyric acid (0.79 mg) and **11b** (1.45 g) as colorless crystals, mp 79—82 °C. IR (KBr) cm^{-1}: 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J=7 Hz), 2.01 (2H, quintet, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.74 (2H, t, J=7 Hz), 2.78—2.98 (1H, m), 5.16 (2H, s), 5.39 (1H, dd, J=10, 11 Hz), 6.22 (1H, d, J=11 Hz), 6.94 (2H, d, J=8 Hz), 7.06 (1H, s), 7.20 (2H, d, J=8 Hz), 7.26—7.42 (2H, m), 7.56 (1H, t, J=8 Hz), 7.58 (1H, d, J=8 Hz), 7.68 (2H, d, J=

8 Hz), 7.81 (1H, d, J=1 Hz), 8.37 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 480 $(M-H)^-$.

4-[1-[3-(3-Isobutylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (12) Following the procedure described above for **4a**, methyl 3-(3-formylphenoxymethyl)benzoate (**12a**) (3.15 g, 89.0%) was prepared from 3-hydroxybenzaldehyde (1.6 g) and methyl 3-(bromomethyl)benzoate (3.0 g). ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.19 (2H, s), 7.26 (1H, m), 7.4—7.6 (4H, m), 7.64 (1H, dd, J=1, 8 Hz), 8.01 (1H, dd, J=1, 8 Hz), 8.14 (1H, t, J=1 Hz).

Following the procedure described above for **10a**, methyl 3-[3-(2-methyl-1-propenyl)phenoxymethyl]benzoate (**12b**) (2.25 g, 63.7%) was prepared from **12a** (2.8 g) and isopropyltriphenylphosphonium iodide (5.82 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, d, J=1 Hz), 1.87 (3H, d, J=1 Hz), 3.92 (1H, s), 5.10 (2H, s), 6.22 (1H, br s), 6.77—6.88 (3H, m), 7.23 (1H, t, J=8 Hz), 7.45 (1H, t, J=1, 8 Hz), 7.63 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.11 (1H, d, J=1 Hz).

12b (2.5 g) was hydrogenated over 5% Pd–C (250 mg) under H_2 (4 atm) to give methyl 3-(3-isobutylphenoxymethyl)benzoate (**12c**) (2.57 g, 102.1%) as an oil, which was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.70—1.94 (1H, m), 2.44 (2H, d, J=7 Hz), 3.91 (3H, s), 5.08 (2H, s), 6.75—6.80 (3H, m), 7.18 (1H, dd, J=8, 10 Hz), 7.45 (1H, t, J=8 Hz), 7.63 (1H, dd, J=1, 8 Hz), 8.00 (1H, dd, J=1, 8 Hz), 8.12 (1H, t, J=1 Hz).

Following the procedure described above for **5b**, **12c** (2.57 g) was hydrolyzed with 1 N NaOH to give 3-(3-isobutylphenoxymethyl)benzoic acid (**12d**) (1.80 g, 73.5%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.76—2.00 (1H, m), 2.46 (2H, d, J=7 Hz), 5.10 (2H, s), 6.73—6.85 (3H, m), 7.20 (1H, dd, J=8, 10 Hz), 7.50 (1H, t, J=8 Hz), 7.72 (1H, dd, J=1, 8 Hz), 8.09 (1H, dd, J=1, 8 Hz), 8.19 (1H, t, J=1 Hz).

Following the procedure described above for **2c**, phenyl 3-(3-isobutylphenoxymethyl)benzoate (**12e**) (2.15 g, 97.0%) was prepared from **12d** (1.75 g). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.76—2.00 (1H, m), 2.44 (2H, d, J=7 Hz), 5.13 (2H, s), 6.72—6.87 (3H, m), 7.14—7.60 (6H, m), 7.72 (1H, dd, J=1, 8 Hz), 8.18 (1H, dd, J=1, 8 Hz), 8.28 (1H, t, J=1 Hz).

Following method A, **12** (1.45 g, 50.2%) was prepared from 1*H*-indole-3-butyric acid (1.25 g) and **12e** (2.22 g) as colorless crystals, mp 81—83 °C. IR (KBr) cm^{-1}: 1710, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (6H, d, J=7 Hz), 1.70—1.92 (1H, m), 2.06 (2H, quintet, J=7 Hz), 2.45 (2H, t, J=7 Hz), 2.47 (2H, t, J=7 Hz), 2.76 (2H, t, J=7 Hz), 5.16 (2H, s), 6.75—6.87 (3H, m), 7.09 (1H, s), 7.20—7.77 (7H, m), 7.83 (1H, s), 8.40 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 468 $(M-H)^-$.

4-[1-[3-(2-Isobutylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (13) Following the procedure described above for **4a**, methyl 3-(2-formylphenoxymethyl)benzoate (**13a**) (2.76 g, 77.8%) was prepared from 2-hydroxybenzaldehyde (1.6 g) and methyl 3-(bromomethyl)benzoate (3.0 g). ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 5.22 (2H, s), 6.98—7.12 (2H, m), 7.42—7.72 (3H, m), 7.88 (1H, dd, J=1, 8 Hz), 8.05 (1H, d, J=8 Hz), 8.12 (1H, br s), 10.58 (1H, s).

Following the procedure described above for **10a**, methyl 3-[2-(2-methyl-1-propenyl)phenoxymethyl]benzoate (**13b**) (2.17 g, 73.3%) was prepared from **13a** (2.70 g) and isopropyltriphenylphosphonium iodide (6.48 g). ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, d, J=1 Hz), 1.92 (3H, d, J=1 Hz), 3.93 (1H, s), 5.11 (2H, s), 6.39 (1H, br s), 6.82—7.00 (2H, m), 7.10—7.25 (2H, m), 7.44 (1H, t, J=8 Hz), 7.63 (1H, d, J=1, 8 Hz), 7.99 (1H, d, J=8 Hz), 8.10 (1H, s).

13b (2.14 g) was hydrogenated over 5% Pd–C (600 mg) under H_2 (3 atm) to give methyl 3-(2-isobutylphenoxymethyl)benzoate (**13c**) (1.99 g, 92.6%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=7 Hz), 1.80—2.10 (1H, m), 2.55 (2H, d, J=7 Hz), 3.92 (3H, s), 5.10 (2H, s), 6.82—6.98 (2H, m), 7.08—7.18 (2H, m), 7.46 (1H, t, J=8 Hz), 7.64 (1H, d, J=8 Hz), 8.00 (1H, d, J=8 Hz), 8.12 (1H, s).

Following the procedure described above for **5b**, **13c** (1.97 g) was hydrolyzed with 1 N NaOH to give 3-(2-isobutylphenoxymethyl)benzoic acid (**13d**) (1.42 g, 75.7%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=7 Hz), 1.85—2.10 (1H, m), 2.59 (2H, d, J=7 Hz), 5.12 (2H, s), 6.80—6.95 (2H, m), 7.08—7.22 (2H, m), 7.50 (1H, t, J=8 Hz), 7.70 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.21 (1H, s).

Following the procedure described above for **2c**, phenyl 3-(2-isobutylphenoxymethyl)benzoate (**13e**) (1.66 g, 93.5%) was prepared from **13d** (1.40 g). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.85—2.12 (1H, m), 2.58 (2H, d, J=7 Hz), 5.18 (2H, s), 6.83—6.98 (2H, m), 7.08—7.35 (5H, m), 7.35—7.63 (3H, m), 7.72 (1H, d, J=8 Hz), 8.18 (1H, d, J=8 Hz), 8.30 (1H, s).

Following method A, **13** (1.66 g, 78.7%) was prepared from 1*H*-indole-3-butyric acid (1.0 g) and **13e** (1.62 g) as colorless crystals, mp 87—89 °C. IR (KBr) cm^{-1}: 1715, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, d, J=7 Hz), 1.81—2.15 (3H, m), 2.44 (2H, t, J=7 Hz), 2.58 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 5.18 (2H, s), 6.83—7.02 (2H, m), 7.02—7.25 (3H, m), 7.25—7.50 (2H, m), 7.50—7.90 (5H, m), 8.40 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 468 $(M-H)^-$.

4-[1-[3-[3-(Isopropyloxy)phenoxymethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (14) Following the procedure described above for **4a**, methyl 3-[3-(isopropyloxy)phenoxymethyl]benzoate (**14a**) (2.15 g, 78.4%) was prepared from 3-(isopropyloxy)phenol (1.39 g) and methyl 3-(bromomethyl)-benzoate (2.09 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (6H, d, J=7 Hz), 3.93 (3H, s), 4.54 (1H, septet, J=7 Hz), 5.08 (2H, s), 6.45—6.62 (3H, m), 7.10—7.20 (1H, m), 7.45 (1H, t, J=8 Hz), 7.65 (1H, d, J=8 Hz), 8.01 (1H, d, J=8 Hz), 8.10 (1H, br s).

Following the procedure described above for **4b**, **14a** (2.14 g) was hydrolyzed with 1 N NaOH to give 3-[3-(isopropyloxy)phenoxymethyl]benzoic acid (**14b**) (1.79 g, 87.9%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J=7 Hz), 4.54 (1H, septet, J=7 Hz), 5.10 (2H, s), 6.48—6.64 (3H, m), 7.10—7.25 (1H, m), 7.52 (1H, t, J=8 Hz), 7.70 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 8.19 (1H, br s).

Following the procedure described above for **2c**, phenyl 3-[3-(isopropyloxy)phenoxymethyl]benzoate (**14c**) (676 mg, 53.5%) was prepared from **14b** (1.0 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J=7 Hz), 4.52 (1H, septet, J=7 Hz), 5.12 (2H, s), 6.43—6.62 (3H, m), 7.10—7.34 (4H, m), 7.34—7.60 (3H, m), 7.72 (1H, m), 8.16 (1H, d, J=8 Hz), 8.25 (1H, br s).

Following method A, **14** (462 mg, 52.7%) was prepared from 1*H*-indole-3-butyric acid (378 mg) and **14c** (666 mg) as colorless crystals, mp 80—82 °C. IR (KBr) cm^{-1}: 1715, 1675. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, d, J=7 Hz), 1.90—2.13 (2H, m), 2.42 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 4.51 (1H, septet, J=7 Hz), 5.11 (2H, s), 6.45—6.60 (3H, m), 7.08 (1H, s), 7.10—7.25 (1H, m), 7.28—7.48 (2H, m), 7.48—7.63 (2H, m), 7.63—7.74 (2H), 7.81 (1H, br s), 8.38 (1H, m). ESI-MS m/z: 468 $(M-H)^-$.

4-[1-[3-[3-(Dimethylaminocarbonyl)phenoxymethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (15) Following the procedure described above for **4a**, methyl 3-[3-(*N*,*N*-dimethylaminocarbonyl)phenoxymethyl]benzoate (**15a**) (1.5 g, 79.2%) was prepared from *N*,*N*-dimethyl-3-hydroxybenzamide (1.0 g) and methyl 3-(bromomethyl)benzoate (1.39 g). ^{1}H-NMR ($CDCl_3$) δ: 2.97 (3H, br s), 3.09 (3H, br s), 3.94 (3H, s), 5.12 (2H, s), 6.95—7.08 (3H, m), 7.32 (1H, t, J=8 Hz), 7.48 (1H, t, J=8 Hz), 7.65 (1H, d, J=8 Hz), 8.00 (1H, d, J=8 Hz), 8.11 (1H, br s).

Following the procedure described above for **5b**, **15a** (1.50 g) was hydrolyzed with 1 N NaOH to give 3-[3-(*N*,*N*-dimethylaminocarbonyl)phenoxymethyl]benzoic acid (**15b**) (1.14 g, 79.2%) as colorless crystals. ^{1}H-NMR ($CDCl_3$: CD_3OD=10 : 1) δ: 2.97 (3H, s), 3.11 (3H, s), 5.14 (2H, s), 6.95—7.13 (3H, m), 7.33 (1H, t, J=8 Hz), 7.47 (1H, t, J=8 Hz), 7.66 (1H, d, J=8 Hz), 8.04 (1H, d, J=8 Hz), 8.16 (1H, s).

Following the procedure described above for **2c**, phenyl 3-[3-(*N*,*N*-dimethylaminocarbonyl)phenoxymethyl]benzoate (**15c**) (1.38 g, 100%) was prepared from **15b** (1.10 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (3H, s), 3.10 (3H, s), 5.16 (2H, s), 6.93—7.11 (3H, m), 7.11—7.63 (7H, m), 7.72 (1H, d, J=8 Hz), 8.19 (1H, d, J=8 Hz), 8.28 (s, 1H).

Following method A, **15** (0.9 g, 50.6%) was prepared from 1*H*-indole-3-butyric acid (755 mg) and **15c** (1.38 g) as white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.98 (2H, quintet, J=7 Hz), 2.32 (2H, t, J=7 Hz), 2.69 (2H, t, J=7 Hz), 3.02 (3H, br s), 3.12 (3H, br s), 5.18 (2H, s), 7.00—7.12 (4H, m), 7.32 (1H, d, J=8 Hz), 7.36 (1H, s), 7.42 (1H, dt, J=1, 8 Hz), 7.56—7.67 (3H, m), 7.76—7.82 (2H, m), 8.49 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 483 $(M-H)^-$.

4-[1-[3-(3-Bromophenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (16) Following the procedure described above for **4a**, methyl 3-(3-bromophenoxymethyl)benzoate (**16a**) (2.25 g, 80.3%) was prepared from 3-bromophenol (1.51 g) and methyl 3-(bromomethyl)benzoate (2.0 g). ^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 5.09 (2H, s), 6.85—6.95 (1H, m), 7.05—7.65 (4H, m), 7.95—8.10 (3H, m).

Following the procedure described above for **5b**, **16a** (2.15 g) was hydrolyzed with 1 N NaOH to give 3-(3-bromophenoxymethyl)benzoic acid (**16b**) (1.64 g, 79.3%) as colorless crystals. ^{1}H-NMR ($CDCl_3$: CD_3OD= 10 : 1) δ: 5.10 (2H, s), 6.85—6.98 (1H, m), 7.02—7.20 (3H, m), 7.50 (1H, t, J=8 Hz), 7.65 (1H, d, J=8 Hz), 8.02 (1H, d, J=8 Hz), 8.12 (1H, br s).

Following the procedure described above for **2c**, phenyl 3-(3-bromophenoxymethyl)benzoate (**16c**) (1.80 g) was prepared from **16b** (1.5 g, 79.7%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 5.12 (2H, s), 6.85—7.00 (1H, m), 7.05—7.35 (6H, m), 7.35—7.65 (3H, m), 7.70 (1H, d, J=8 Hz), 8.18 (1H, d, J=8 Hz), 8.25 (1H, br s).

Following method A, **16** (1.72 g, 74.2%) was prepared from 1*H*-indole-3-butyric acid (965 mg) and **16c** (1.80 g) as colorless crystals, mp 93—95 °C. IR (KBr) cm^{-1}: 1715, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.15 (2H, m), 2.42

(2H, t, J=7 Hz), 2.70 (2H, t, J=7 Hz), 5.10 (2H, s), 6.83—6.95 (1H, m), 7.00—7.20 (4H, m), 7.20—7.50 (2H, m), 7.50—7.75 (4H, m), 7.80 (1H, br s), 8.38 (1H, d, J=8 Hz). ESI-MS m/z: 490 $(M-H)^-$.

4-[1-[2,3-Dimethyl-5-(3-isobutylphenoxymethyl)benzoyl]-1*H*-indol-3-yl]butyric Acid (17) To a solution of 3,4-dimethylbenzoic acid (10.0 g, 6.66 mmol) in acetic acid (300 ml) were added nitric acid (47 ml), water (33 ml) and bromine (11.7 g, 7.33 mmol) at 20 °C, followed by an aqueous solution (70 ml) of silver nitrate (14.7 g, 8.66 mmol) over 1 h. The reaction mixture was partitioned between EtOAc and water, and the organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by recrystallization (EtOH) to give 3-bromo-4,5-dimethylbenzoic acid (**17a**) (6.16 g, 40.4%) as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.46 (3H, s), 7.82 (1H, d, J=1 Hz), 8.28 (1H, d, J=1 Hz).

A 1 M solution of BH_3 in THF (40.5 ml, 40.5 mmol) was added to a solution of **17a** (4.22 g, 18.4 mmol) in THF (20 ml) at 0 °C and the reaction mixture was allowed to warm up to 20 °C. After stirring for 2 h, the reaction mixture was partitioned between Et_2O and 1 N HCl. The organic layer was washed with water and brine and dried over $MgSO_4$. Evaporation of solvent gave 3-bromo-4,5-dimethylbenzyl alcohol (**17b**) (4.00 g, 100%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.36 (3H, s), 4.60 (2H, s), 7.09 (1H, d, J=1 Hz), 7.42 (1H, d, J=1 Hz).

Triphenylphosphine (7.23 g, 27.5 mmol) was added to a mixture of the alcohol **17b** (3.95 g, 18.4 mmol) and CBr_4 (9.14 g , 27.5 mmol) in Et_2O (100 ml) at 0 °C. The reaction mixture was allowed to warm up to 20 °C and stirred for 2 h. The precipitates were filtered off and the filtrate was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) to give 3-bromo-4,5-dimethylbenzyl bromide (**17c**) (4.15 g, 81.1%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.46 (3H, s), 4.38 (2H, s), 7.12 (1H, d, J=1 Hz), 7.45 (1H, d, J=1 Hz).

A mixture of **17c** (1.80 g, 6.45 mmol), 3-isobutylphenol (1.07 g, 7.12 mmol) and K_2CO_3 (1.79 g, 13.0 mmol) in DMF (20 ml) was stirred at 20 °C for 3 h, and partitioned between Et_2O and 1 N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc in hexane) to give 3-bromo-4,5-dimethylbenzyl 3-isobutylphenyl ether (**17d**) (2.13 g, 94.6%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.75—1.98 (1H, m), 2.33 (3H, s), 2.37 (3H, s), 2.44 (2H, d, J=7 Hz), 4.93 (2H, s), 6.72—6.84 (3H, m), 7.14—7.24 (2H, m), 7.50 (1H, d, J=1 Hz).

A mixture of **17d** (2.00 g, 5.76 mmol), Mg (280 mg, 11.5 mmol) and 1,2-dibromoethane (540 mg, 2.88 mmol) in THF (20 ml) was stirred under reflux for 2 h, and cooled to 20 °C. After addition of dry ice (2 g), the reaction mixture was poured into a mixture of Et_2O and 1 N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by recrystallization (EtOAc–hexane) to give 2,3-dimethyl-5-(3-isobutylphenoxymethyl)benzoic acid (**17e**) (1.56 g, 86.7%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.65—1.98 (1H, m), 2.37 (3H, s), 2.45 (2H, d, J=7 Hz), 2.55 (3H, s), 5.02 (2H, s), 6.72—6.85 (3H, m), 7.18 (1H, dd, J=6, 8 Hz), 7.45 (1H, d, J=1 Hz), 7.90 (1H, d, J=1 Hz).

Following the procedure described above for **3c**, phenyl 2,3-dimethyl-5-(3-isobutylphenoxymethyl)benzoate (**17f**) (1.37 g, 100%) was prepared from **17e** (1.1 g). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J=7 Hz), 1.80—2.00 (1H, m), 2.42 (3H, s), 2.48 (2H, d, J=7 Hz), 2.58 (3H, s), 5.08 (2H, s), 6.78—6.90 (3H, m), 7.20—7.32 (4H, m), 7.45—7.52 (3H, m), 8.02 (1H, d, J=1 Hz).

Following method A, **17** (1.45 g, 82.8%) was prepared from 1*H*-indole-3-butyric acid (717 mg) and **17f** (1.37 g) as colorless crystals, mp 100—101 °C. IR (KBr) cm^{-1}: 1710, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, J=7 Hz), 1.75—2.10 (3H, m), 2.23 (3H, s), 2.38 (3H, s), 2.43—2.52 (4H, m), 2.72 (2H, t, J=7 Hz), 5.07 (2H, s), 6.75—6.90 (4H, m), 7.20 (1H, dd, J=6, 8 Hz), 7.30—7.50 (5H, m), 7.58 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 496 $(M-H)^-$.

4-[1-[4-[Bis(4-isobutylphenyl)methoxy]benzoyl]-1*H*-indol-3-yl]butyric Acid (18) A mixture of 4-(methoxymethoxy)benzoic acid (10.0 g, 58.8 mmol), phenol (16.8 g, 176 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (22.5 g, 11.4 mmol) in CH_2Cl_2 (200 ml) was stirred under reflux for 15 h. After evaporation of solvent, the residue was partitioned between EtOAc and 1 N HCl. The organic layer was washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was redissolved in hexane and the solution washed with water, dried over $MgSO_4$, and evaporated to give phenyl 4-(methoxymethoxy)benzoate (**18a**) (4.00 g, 25.0%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (3H, s), 5.25 (3H, s), 7.12 (2H, d, J=10 Hz), 7.15—7.30 (3H, m), 7.45 (5H, m), 8.15 (2H, d, J=10 Hz).

Following method A, 4-[1-[4-(methoxymethoxy)benzoyl]-1*H*-indol-3-yl]butyric acid (**18b**) (5.76 g, 100%) was prepared from 1*H*-indole-3-butyric acid (2.88 g) and **18a** (3.66 g). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (2H, m), 2.45 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 3.52 (3H, s), 5.25 (2H, s), 6.70—7.40 (5H, m), 7.55 (1H, m), 7.70 (2H, d, J=8 Hz), 8.45 (1H, m).

A mixture of **18b** (2.50 g, 6.80 mmol), benzyl bromide (1.81 g, 10.2 mmol) and K_2CO_3 (2.82 g, 20.4 mmol) in DMF (30 ml) was stirred at 20 °C for 6 h. The reaction mixture was diluted with EtOAc, washed with 1 N HCl, water, aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2) to give benzyl 4-[1-[4-(methoxymethoxy)benzoyl]-1*H*-indol-3-yl]butyrate (**18c**) (3.02 g, 96.9%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (2H, m), 2.45 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 3.52 (3H, s), 5.10 (2H, s), 5.28 (2H, s), 7.10—7.20 (3H, m), 7.25—7.40 (7H, m), 7.55 (1H, m), 7.70 (2H, d, J=8 Hz), 8.85 (1H, m).

18c (572 mg, 1.25 mmol) was dissolved in CF_3CO_2H (12 ml) and the mixture was stirred at 25 °C for 15 min. After evaporation of solvent, the residue was dissolved in EtOAc, washed with aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 2) to give benzyl 4-[1-(4-hydroxybenzoyl)-1*H*-indol-3-yl]butyrate (**18d**) (350 mg, 67.7%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, m), 2.50 (2H, t, J=7 Hz), 2.80 (2H, t, J=7 Hz), 5.15 (2H, s), 6.98 (2H, d, J=10 Hz), 7.20—7.60 (7H, m), 7.60 (1H, m), 7.65 (2H, d, J=10 Hz), 7.70 (2H, d, J=8 Hz), 8.40 (1H, m).

A solution of **18d** (1.75 g, 4.23 mmol) in DMF (10 ml) was added to a suspension of NaH (60% dispersion in mineral oil, 203 mg, 5.08 mmol) in DMF (10 ml) at −40 °C, and the mixture was stirred for 15 min. A solution of bromobis(4-isobutylphenyl)methane (1.68 g, 4.70 mmol) in DMF (10 ml) was added to the reaction mixture at −40 °C, and the resulting mixture was allowed to warm up to 0 °C. After stirring for 4 h at 0 °C, the mixture was poured into chilled 1 N HCl, and extracted with EtOAc. The extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 5) to give benzyl 4-[1-[4-[bis(4-isobutylphenyl)methoxy]benzoyl]-1*H*-indol-3-yl]butyrate (**18e**) (502 mg, 30.0%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (12H, d, J=7 Hz), 1.85 (2H, m), 2.05 (2H, m), 2.35—2.50 (6H, m), 2.70 (2H, t, J=7 Hz), 5.10 (2H, s), 6.28 (1H, s), 7.00—7.40 (18H, m), 7.50 (1H, m), 7.65 (1H, m), 8.30 (1H, m).

18e (500 mg, 0.723 mmol) was hydrogenated in THF (10 ml) over 10% Pd–C (50 mg) under H_2 (1 atm) at 20 °C for 8 h to give **18** (162 mg, 37.3%) as a white powder, mp 70—72 °C. IR (KBr) cm^{-1}: 1715, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (12H, d, J=7 Hz), 1.80 (2H, m), 2.05 (2H, m), 2.35—2.50 (6H, m), 2.72 (2H, t, J=7 Hz), 6.25 (1H, s), 7.00—7.20 (7H, m), 7.25—7.40 (6H, m), 7.55 (1H, m), 7.65 (2H, d, J=10 Hz), 8.30 (1H, m). ESI-MS m/z: 600 $(M-H)^-$.

4-[1-[3-[Bis(4-isobutylphenyl)methoxy]benzoyl]-1*H*-indol-3-yl)butyric Acid (19) Following the procedure described above for **2c**, phenyl 3-(methoxymethoxy)benzoate (**19a**) (3.17 g, 74.4%) was prepared from 3-(methoxymethoxy)benzoic acid (3.0 g). ^{1}H-NMR ($CDCl_3$) δ: 3.51 (3H, s), 5.26 (3H, s), 7.20—7.50 (7H, m), 7.85—7.90 (2H, m).

Following method A, 4-[1-[3-(methoxymethoxy)benzoyl]-1*H*-indol-3-yl]butyric acid (**19b**) (2.96 g, 61.7%) was prepared from 1*H*-indole-3-butyric acid (2.42 g) and **19a** (3.07 g) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (2H, quintet, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.66 (2H, t, J=7 Hz), 3.50 (3H, s), 5.36 (2H, s), 7.10 (1H, s), 7.20—7.60 (7H, m), 8.40 (1H, d, J=8 Hz).

To a solution of **19b** (1.4 g, 3.81 mmol) in 1,4-dioxane (10 ml) was added 4 N HCl in 1,4-dioxane (4 ml, 16.0 mmol) at 20 °C. After stirring for 6 h, the reaction mixture was partitioned between ether and water. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was triturated with IPE to give 4-[1-(3-hydroxybenzoyl)-1*H*-indol-3-yl]butyric acid (**19c**) (1.0 g, 81.2%) as colorless crystals. ^{1}H-NMR ($CDCl_3$: CD_3OD=10 : 1) δ: 2.02 (2H, quintet, J=7 Hz), 2.40 (2H, t, J=7 Hz), 2.75 (2H, t, J=7 Hz), 3.50 (3H, s), 7.05—7.20 (3H, m), 7.30—7.45 (4H, m), 7.60—7.70 (1H, m), 8.38 (1H, dd, J=2, 8 Hz).

Following the procedure described above for **18e**, **19** (370 mg, 41.5%) was prepared from **19c** (480 mg) and bromobis(4-isobutyphenyl)methane (640 mg) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.86 (2H, m), 2.02 (2H, m), 2.35—2.50 (6H, m), 2.62 (2H, t, J=7 Hz), 6.23 (1H, s), 7.00 (1H, s), 7.10 (4H, d, J=8 Hz), 7.15—7.40 (10H, m), 7.58 (1H, m), 8.47 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 600 $(M-H)^-$.

4-[1-[3-[Bis(4-isobutylphenyl)methylthio]benzoyl]-1*H*-indol-3-yl]bu-

tyric Acid (20) A mixture of 3-bromothiophenol (1.0 g, 5.29 mmol), bromobis(4-isobutylphenyl)methane (2.0 g, 5.55 mmol) and K_2CO_3 (1.46 g, 10.5 mmol) in DMF (10 ml) was stirred at 20 °C for 1 h, and partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to give bis(4-isobutylphenyl)-methyl 3-bromophenyl sulfide (**20a**) (1.60 g, 64.7%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.84 (2H, m), 2.44 (4H, t, J=7 Hz), 5.48 (1H, s), 6.96—7.15 (6H, m), 7.20—7.35 (6H, m).

Following the procedure described above for **17e**, 3-[bis(4-isobutylphenyl)methylthio]benzoic acid (**20b**) (1.15 g, 82.8%) was prepared from **20a** (1.50 g). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.82 (2H, m), 2.42 (4H, t, J=7 Hz), 5.52 (1H, s), 7.07 (4H, d, J=8 Hz), 7.15—7.45 (6H, m), 7.82 (1H, d, J=8 Hz), 7.95 (1H, s).

Following the procedure described above for **2c**, phenyl 3-[bis(4-isobutylphenyl)methylthio]benzoate (**20c**) (1.32 g) was prepared from **20b** (1.0 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (12H, d, J=7 Hz), 1.86 (2H, m), 2.45 (4H, t, J=7 Hz), 5.62 (1H, s), 7.11 (4H, d, J=8 Hz), 7.15—7.50 (11H, m), 7.95 (1H, d, J=8 Hz), 8.10 (1H, d, J=8 Hz).

Following method A, **20** (0.65 g, 46.3% from **20b**) was prepared from 1*H*-indole-3-butyric acid (519 mg) and **20c** (1.30 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (12H, d, J=7 Hz), 1.80 (2H, m), 2.02 (2H, m), 2.36—2.50 (6H, m), 2.72 (2H, t, J=7 Hz), 5.55 (1H, s), 6.95 (1H, s), 7.05 (4H, d, J=8 Hz), 7.20—7.50 (9H, m), 7.50—7.60 (2H, m), 8.26 (1H, d, J=8 Hz). ESI-MS m/z: 616 $(M-H)^-$.

4-[1-[3-[2,2-Bis(4-isobutylphenyl)ethyl]benzoyl]-1*H*-indol-3-yl]butyric Acid (21) A 1.6 M solution of BuLi in hexane (10.8 ml, 16.2 mmol) was added to a solution of bis(4-isobutylphenyl)methane (4.0 g, 14.3 mmol) in THF (20 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, and 3-bromobenzyl bromide (4.2 g, 16.8 mmol) was added. After stirring at 0 °C for 30 min, the mixture was partitioned between EtOAc and 1 N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to give 1-(3-bromophenyl)-2,2-bis(4-isobutylphenyl)ethane (**21a**) (3.10 g, 44.0%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.82 (2H, m), 2.41 (4H, t, J=7 Hz), 3.27 (2H, d, J=7 Hz), 4.09 (1H, t, J=7 Hz), 6.85 (1H, d, J=7 Hz), 7.00—7.30 (11H, m).

Following the procedure described above for **17e**, 3-[2,2-bis(4-isobutylphenyl)ethyl]benzoic acid (**21b**) (2.12 g, 74.7%) was prepared from **21a** (3.08 g). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (12H, d, J=7 Hz), 1.78 (2H, m), 2.36 (4H, t, J=7 Hz), 3.20 (2H, d, J=7 Hz), 4.07 (1H, t, J=7 Hz), 6.70—7.20 (10H, m), 7.60—7.80 (2H, m).

Following the procedure described above for **2c**, phenyl 3-[2,2-bis(4-isobutylphenyl)ethyl]benzoate (**21c**) (2.51 g, 100%) was prepared from **21b** (2.12 g) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (12H, d, J=7 Hz), 1.80 (2H, m), 2.40 (4H, t, J=7 Hz), 3.41 (2H, d, J=7 Hz), 4.17 (1H, t, J=7 Hz), 7.02 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 7.12—7.30 (5H, m), 7.30—7.50 (2H, m), 7.88 (1H, br s), 7.95 (1H, d, J=8 Hz).

Following method A, **21** (76 mg, 90.2%) was prepared from 1*H*-indole-3-butyric acid (29 mg) and **21c** (69 mg) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (12H, d, J=7 Hz), 1.75 (2H, m), 2.01 (2H, m), 2.30—2.50 (6H, m), 2.73 (2H, t, J=7 Hz), 3.39 (2H, d, J=7 Hz), 4.16 (2H, t, J=7 Hz), 5.55 (1H, s), 7.00 (4H, d, J=8 Hz), 7.10 (4H, d, J=8 Hz), 7.12—7.40 (5H, m), 7.40—7.50 (2H, m), 7.55 (1H, m), 8.25 (1H, m). ESI-MS m/z: 598 $(M-H)^-$.

4-[1-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-1*H*-indol-3-yl]butyric Acid (22) A mixture of 1*H*-indole-3-butyric acid (25 g, 123 mmol), benzyl bromide (21 g, 123 mmol) and K_2CO_3 (20 g, 150 mmol) in DMF (150 ml) was stirred at 20 °C for 4 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was crystallized (hexane) to give benzyl 4-(1*H*-indol-3-yl)butyrate (**22a**) (33.9 g, 93.9%), mp 55—56 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, m), 2.43 (2H, t, J=7 Hz), 2.70 (2H, t, J=7 Hz), 5.10 (2H, s), 6.90 (1H, d, J=2 Hz), 7.10 (1H, dt, J=2, 8 Hz), 7.16 (1H, dt, J=2, 8 Hz), 7.30 (1H, m), 7.33 (5H, s), 7.58 (1H, d, J=8 Hz), 7.90 (1H, br s).

To a solution of **22a** (33.7 g, 115 mmol) in CH_2Cl_2 (400 ml) were added triethylamine (30 ml, 220 mmol), 4-dimethylaminopyridine (1.22 g, 16 mmol) and 3-nitrobenzoyl chloride (30 g, 160 mmol). The reaction mixture was stirred under reflux for 16 h and 3-nitrobenzoyl chloride (10.5 g, 55 mmol) and triethylamine (5 ml, 35 mmol) were added. The reaction mixture was stirred under reflux for 19 h and 3-dimethylaminopropylamine (15 ml, 120 mmol) was added at 0 °C. The mixture was washed with 1 N HCl and water, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give benzyl 4-[1-(3-nitrobenzoyl)-1*H*-indol-3-yl]butyrate (**22b**) (47.6 g, 93.6%) as a pale yellow solid, mp 89—90 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (2H, m), 2.40 (2H, t, J=7 Hz), 2.70 (2H, t, J=7 Hz), 5.06 (2H, s), 6.93 (1H, s), 7.30 (5H, s), 7.35 (1H, m), 7.40 (1H, dt, J=2, 8 Hz), 7.60 (1H, dd, J=2, 8 Hz), 7.72 (1H, t, J=8 Hz), 8.05 (1H, dd, J=2, 8 Hz), 8.38 (1H, d, J=8 Hz), 8.48 (1H, m), 8.60 (1H, m).

10% Pd–C (4.7 g) was added to a solution of **22b** (473 g, 107 mmol) in a mixture of MeOH (500 ml) and 1,4-dioxane (500 ml) and the mixture was stirred under H_2 (1 atm) at 20 °C for 17 h. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The residue was triturated with 1 N HCl (120 ml) to give 4-[1-(3-aminobenzoyl)-1*H*-indol-3-yl]butyric acid hydrochloride (**22c**) (34.75 g, 90.5%) as crystals, mp 181—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (2H, m), 2.37 (2H, t, J=7 Hz), 2.70 (2H, t, J=7 Hz), 7.00 (1H, s), 7.35 (3H, m), 7.50—7.80 (3H, m), 8.35 (1H, dt, J=2, 8 Hz).

To a solution of **22c** (14.5 g, 40 mmol) in CH_2Cl_2 (300 ml) were added diisopropylethylamine (22 ml, 126 mmol) and bromobis(4-isobutylphenyl)-methane (14.5 g, 40 mmol). The mixture was stirred at 20 °C for 15 h and diisopropylethylamine (7 ml, 40 mmol) and bromobis(4-isobutyphenyl)-methane (2.0 g, 5.6 mmol) were added. After stirring for 6 h, the mixture was acidified with 1 N HCl. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) to give **22** (23.2 g, 96.5%) as a white powder, mp 74—76 °C. IR (KBr) cm^{-1}: 1710, 1685. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (12H, d, J=7 Hz), 1.77—1.93 (2H, m), 2.03 (2H, quintet, J=7 Hz), 2.46 (2H, t, J=7 Hz), 2.48 (4H, d, J=7 Hz), 2.73 (2H, t, J=7 Hz), 5.54 (1H, s), 6.77 (1H, dd, J=1, 8 Hz), 6.94 (1H, t, J=1 Hz), 7.00 (1H, d, J=8 Hz), 7.12 (1H, s), 7.13 (4H, d, J=8 Hz), 7.22—7.43 (7H, m), 7.58 (1H, dd, J=1, 8 Hz), 8.40 (1H, dd, J=1, 8 Hz). ESI-MS m/z: 599 $(M-H)^-$.

4-[1-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-5-chloro-1*H*-indol-3-yl]butyric Acid (23) Methyl succinyl chloride (7.3 ml, 59.3 mmol) was added to a suspension of $AlCl_3$ (12.9 g, 96.8 mmol) in CH_2Cl_2 (100 ml) at 20 °C over 20 min. The reaction mixture was stirred at the same temperature for 1 h and a solution of 5-chloro-1*H*-indole (5.0 g, 33.0 mmol) in CH_2Cl_2 (50 ml) was added. After stirring for 3 h at 25 °C, the reaction mixture was poured into a mixture of 1 N HCl and ice. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) to give methyl 4-(5-chloro-1*H*-indol-3-yl)-4-oxobutyrate (**23a**) (3.33 g, 38.0%) as colorless crystals, mp 150—153 °C. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.28 (2H, t, J=7 Hz), 3.24 (2H, t, J=7 Hz), 3.72 (3H, s), 7.20 (1H, dd, J=2, 8 Hz), 7.30—7.42 (2H, m), 8.00 (1H, d, J=2 Hz), 8.32 (1H, s).

To a mixture of **23a** (3.00 g, 11.3 mmol) and $NaBH_4$ (855 mg, 22.6 mmol) in THF (30 ml) was added $BF_3 \cdot Et_2O$ (4.2 ml, 34.1 mmol) at 20 °C over 20 min and the reaction mixture was stirred for 3 h. After addition of acetone (3 ml), the mixture was poured into a mixture of EtOAc and 1 N HCl. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography ($CHCl_3$) and recrystallization (EtOAc–hexane) to give methyl 4-(5-chloro-1*H*-indol-3-yl)butyrate (**23b**) (989 mg, 34.8%) as colorless crystals, mp 74—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.13 (2H, m), 2.39 (2H, t, J=7 Hz), 2.76 (2H, t, J=7 Hz), 3.68 (3H, s), 7.00 (1H, d, J=8 Hz), 7.13 (1H, dd, J=2, 8 Hz), 7.28 (1H, d, J=8 Hz), 7.55 (1H, d, J=2 Hz), 8.01 (1H, br s).

Following the procedure described above for **5b**, **23b** (909 mg) was hydrolyzed with 1 N NaOH to give 4-(5-chloro-1*H*-indol-3-yl)butyric acid (**22c**) (752 mg, 87.6%) as colorless crystals, mp 139—141 °C. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 1.98—2.14 (2H, m), 2.40 (2H, t, J=7 Hz), 2.89 (2H, t, J=7 Hz), 7.04 (1H, s), 7.13 (1H, dd, J=2, 8 Hz), 7.28 (1H, d, J=8 Hz), 7.56 (1H, d, J=2 Hz).

Following the procedure described above for **23a**, benzyl 4-(5-chloro-1*H*-indol-3-yl)butyrate (**23d**) (1.40 g, 67.8%) was prepared from **23c** (1.50 g), mp 46—47 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.18 (2H, m), 2.44 (2H, t, J=7 Hz), 2.76 (2H, t, J=7 Hz), 5.14 (2H, s), 6.98 (1H, s), 7.14 (1H, d, J=8 Hz), 7.21—7.51 (6H, m), 7.53 (1H, s), 7.95 (1H, br s).

Following the procedure described above for **22b**, benzyl 4-[5-chloro-1-(3-nitrobenzoyl)-1*H*-indol-3-yl]butyrate (**23e**) (1.51 g, 85.5%) was prepared from **23d** (1.30 g) and 3-nitrobenzoyl chloride (1.47 g) as colorless crystals, mp 134—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (2H, m), 2.45 (2H, t, J=7 Hz), 2.72 (2H, t, J=7 Hz), 5.11 (2H, s), 6.99 (1H, s), 7.30—7.50 (6H, m), 7.56 (1H, d, J=2 Hz), 7.78 (1H, t, J=8 Hz), 8.08 (1H, dd, J=2, 8 Hz), 8.37 (1H, d, J=8 Hz), 8.50 (1H, dd, J=2, 8 Hz), 8.60 (1H, m).

A mixture of **23e** (1.3 g, 2.92 mmol) and 10% Pd–C (400 mg) in a mixture of MeOH (35 ml) and 1,4-dioxane (35 ml) was stirred under H_2 (3 atm) at

20 °C for 4 h. The catalyst was filtered off and the filtrate was evaporated. The residue was purified by silica gel column chromatography (2% MeOH in $CHCl_3$) to give 4-[1-(3-aminobenzoyl)-5-chloro-1*H*-indol-3-yl]butyric acid (**23f**) (731 mg, 70.1%) as pale yellow crystals, mp 139—143 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.15 (2H, m), 2.49 (2H, t, J=7 Hz), 2.73 (2H, t, J=7 Hz), 6.90—7.22 (4H, m), 7.22—7.42 (2H, m), 7.52 (1H, d, J=2 Hz), 8.30 (1H, d, J=8 Hz).

Following the procedure described above for **22**, **23** (803 mg, 61.4%) was prepared from **23f** (700 mg) and bromobis(4-isobutylphenyl)methane (705 mg) as a foam, mp 82—85 °C. IR (KBr) cm^{-1}: 1710, 1690. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.74—1.92 (2H, m), 2.00 (2H, quintet, J=7 Hz), 2.42 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.67 (2H, t, J=7 Hz), 5.00 (1H, s), 6.74 (1H, dd, J=1, 8 Hz), 6.96 (1H, d, J=8 Hz), 7.08 (4H, d, J=8 Hz), 7.18—7.33 (6H, m), 7.45—7.72 (3H, m), 8.26 (1H, m). ESI-MS m/z: 633 (M−H)$^-$.

4-[1-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-2-methyl-1*H*-indol-3-yl]butyric Acid (24) Following the procedure described above for **23a**, methyl 4-(2-methyl-1*H*-indol-3-yl)-4-oxobutyrate (**24a**) (908 mg, 16.2%) was prepared from 2-methyl-1*H*-indole (3 g) and methyl succinyl chloride (3 ml), mp 145—147 °C. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 2.65 (3H, s), 2.80 (2H, t, J=7 Hz), 3.30 (2H, t, J=7 Hz), 3.72 (3H, s), 7.10—7.38 (3H, m), 7.92—8.08 (1H, m).

Following the procedure described above for **23b**, methyl 4-(2-methyl-1*H*-indol-3-yl)butyrate (**24b**) (1.67 g, 88.5%) was prepared from **24a** (2.0 g). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.09 (2H, m), 2.25—2.40 (5H, m), 2.72 (2H, t, J=7 Hz), 3.60 (3H, s), 7.00—7.15 (2H, m), 7.15—7.29 (1H, m), 7.75 (1H, br s).

Following the procedure described above for **5b**, **24b** (1.65 g) was hydrolyzed with 1 N NaOH to give 4-(2-methyl-1*H*-indol-3-yl)butyric acid (**24c**) (1.23 g, 79.1%) as brown crystals, mp 85—87 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.06 (2H, m), 2.26—250 (5H, m), 2.75 (2H, t, J=7 Hz), 6.92 (1H, d, J=8 Hz), 7.00—7.18 (2H, m), 7.18—7.30 (1H, m), 7.40—7.54 (1H, m), 7.70 (1H, br s).

Following method A, 4-[2-methyl-1-(3-nitrobenzoyl)-1*H*-indol-3-yl]butyric acid (**24d**) (749 mg, 80.6%) was prepared from **24c** (600 mg) and phenyl 3-nitrobenzoate (671 mg), mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (2H, m), 2.45 (2H, t, J=7 Hz), 2.72 (2H, t, J=7 Hz), 5.11 (2H, m), 6.99 (1H, m), 7.04 (1H, dt, J=2, 8 Hz), 7.20 (1H, dt, J=2, 8 Hz), 7.52 (1H, d, J=8 Hz), 7.72 (1H, t, J=8 Hz), 8.03 (1H, dd, J=1, 8 Hz), 8.50 (1H, dd, J=1, 8 Hz), 8.58 (1H, d, J=1 Hz).

Following the procedure described above for **23f**, 4-[1-(3-aminobenzoyl)-2-methyl-1*H*-indol-3-yl]butyric acid (**24f**) (490 mg, 89.7%) was prepared from **24d** (600 mg) as a pale yellow foam. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 1.85—2.10 (2H, m), 2.25—2.47 (5H, m), 2.75 (2H, t, J=7 Hz), 6.85—7.35 (7H, m), 7.49 (1H, d, J=8 Hz).

Following the procedure described above for **22**, **24** (720 mg, 61.1%) was prepared from **24f** (587 mg) and bromobis(4-isobutyphenyl)methane (905 mg) as a yellow foam, mp 74—76 °C. IR (KBr) cm^{-1}: 1710, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.74—1.88 (2H, m), 1.97 (2H, quintet, J=7 Hz), 2.26 (3H, s), 2.43 (2H, t, J=7 Hz), 2.45 (4H, d, J=7 Hz), 2.74 (2H, t, J=7 Hz), 5.47 (1H, s), 6.76 (1H, dd, J=1, 8 Hz), 6.91 (1H, t, J=1 Hz), 6.96 (1H, d, J=8 Hz), 7.07 (4H, d, J=8 Hz), 7.10—7.28 (7H, m), 7.46 (2H, m). ESI-MS m/z: 613 (M−H)$^-$.

4-[3-[3-[Bis(4-isobutylphenyl)methylamino]benzoyl]-1*H*-indol-1-yl)butyric Acid (FK143) A solution of 3-nitrobenzoyl chloride (871 mg, 4.69 mmol) in CH_2Cl_2 (2 ml) was added to a suspension of $AlCl_3$ (835 mg, 6.40 mmol) in CH_2Cl_2 (10 ml) at 25 °C. The reaction mixture was stirred at 20 °C for 1 h, and a solution of 1*H*-indole (500 mg, 4.27 mmol) in CH_2Cl_2 (5 ml) was added. After stirring for 1 h at 25 °C, the reaction mixture was poured into a mixture of EtOAc and ice water. The organic layer was separated, washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the solid residue was recrystallized (EtOAc) to give 3-(3-nitrobenzoyl)-1*H*-indole (**25**) (495 mg, 43.6%) as pale red crystals. ^{1}H-NMR ($CDCl_3$: CD_3OD=1 : 1) δ: 7.21—7.35 (2H, m), 7.42—7.55 (1H, m), 7.68—7.79 (2H, m), 8.13 (1H, dd, J=1, 8 Hz), 8.24—8.35 (1H, m), 8.40 (1H, dd, J=1, 8 Hz), 8.60 (1H, t, J=1 Hz).

A mixture of **25** (490 mg, 1.84 mmol), ethyl 4-bromobutyrate (430 mg, 2.21 mmol) and K_2CO_3 (509 mg, 3.68 mmol) in DMF (5 ml) was stirred at 40 °C for 3 h. The reaction mixture was partitioned between EtOAc and 0.1 N HCl, and the organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the solid residue was recrystallized (EtOAc–hexane) to give ethyl 4-[3-(3-nitrobenzoyl)-1*H*-indol-1-yl]butyrate (**26**) (630 mg, 90.0%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ:1.20 (3H, t, J=7 Hz), 2.12—2.40 (4H, m), 4.10 (2H, q, J=7 Hz), 4.30 (2H, t, J=7 Hz), 7.30—7.50 (3H, m), 7.58 (1H, s), 7.70 (1H, t, J=8 Hz), 8.27 (1H, dd, J=1, 8 Hz), 8.35—8.48 (2H, m), 8.68 (1H, d, J=1 Hz).

26 (300 mg, 1.31 mmol) was hydrogenated over 10% Pd–C (200 mg) under H_2 (3 atm) at 20 °C for 45 min to give ethyl 4-[3-(3-aminobenzoyl)-1*H*-indol-1-yl]butyrate (**27**) (459 mg, 86.3%) as a yellow oil. ^{1}H-NMR (CD_3Cl : CD_3OD=1 : 1) δ: 1.22 (3H, t, J=7 Hz), 2.12—2.37 (4H, m), 4.10 (2H, q, J=7 Hz), 4.23 (2H, t, J=7 Hz), 6.90 (1H, dt, J=8, 1 Hz), 7.18—7.45 (6H, m), 7.62 (1H, s), 8.43 (1H, m).

To a solution of **27** (459 mg, 1.13 mmol) in CH_2Cl_2 (10 ml) were added chlorobis(4-isobutylphenyl)methane (497 mg, 1.58 mmol) and iPr_2EtN (0.343 ml, 1.97 mmol). After stirring at 20 °C overnight, the reaction mixture was partitioned between EtOAc and 0.1 N HCl. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (EtOAc : hexane=1 : 10 to 1 : 4) to give ethyl 4-[3-[3-[bis(4-isobutylphenyl)-methylamino]benzoyl]-1*H*-indol-1-yl]butyrate (**28**) (635 mg, 77.2%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.20 (3H, t, J=7 Hz), 1.74—1.94 (2H, m), 2.10—2.32 (4H, m), 2.43 (4H, d, J=7 Hz), 4.10 (2H, q, J=7 Hz), 4.18 (2H, t, J=7 Hz), 5.54 (1H, s), 6.72 (1H, d, J=8 Hz), 7.04—7.42 (14H, m), 7.46 (1H, s), 8.46 (1H, dd, J=2, 8 Hz).

To a solution of **28** (625 mg, 0.99 mmol) in 1,4-dioxane (5 ml) were added 1 N NaOH (1.5 ml) and MeOH (2 ml). After stirring at 20 °C for 14 h, the reaction mixture was acidified with 1 N HCl and extracted with ether. The extract was washed with water and brine, and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by crystallization (EtOH–hexane) to give FK143 (520 mg, 87.5%) as colorless crystals, mp 150—152 °C. IR (KBr) cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (12H, d, J=7 Hz), 1.74—1.94 (2H, m), 2.18 (2H, quintet, J=7 Hz), 2.36 (2H, t, J=7 Hz), 2.44 (4H, d, J=7 Hz), 4.18 (2H, t, J=7 Hz), 5.52 (1H, s), 6.71 (1H, dd, J=1, 8 Hz), 7.04 (1H, t, J=1 Hz), 7.09 (4H, d, J=8 Hz), 7.16 (4H, d, J=8 Hz), 7.22—7.40 (8H, m), 7.45 (1H, s), 8.40—8.46 (1H, m). ESI-MS m/z: 599 (M−H)$^-$. *Anal*. Calcd for $C_{40}H_{44}N_2O_3$: C, 79.97; H, 7.38; N, 4.66. Found: C, 79.60; H, 7.44; N, 4.77.

Biological Data Preparation of Prostatic Enzyme: Rat ventral prostates, removed from 10—20 week old male Wistar rats, dissected free of their capsules, were washed with saline, and stored at −80 °C. Human prostatic tissues from BPH patients who received transurethral prostatectomy were kindly provided by Dr M. Tachibana at Keio University Hospital, and stored at −80 °C. Prostatic enzyme fractions were prepared as previously described in the literature.[11] Frozen tissues were thawed on ice and minced with scissors. Unless specified, all of the following procedures were carried out at 4 °C. The tissues were homogenized with a Polytron homogenizer in 3—4 tissue volumes of medium A (0.32 M sucrose, 0.1 mM dithiothreitol (DTT), and 20 mM sodium phosphate buffer pH 6.5). The homogenates were centrifuged at 1500 ***g*** for 20 min, and the nuclear membrane fractions were precipitated. The pellets were then resuspended in medium A and filtered with gauze. The suspension (3—10 mg/ml) was stored at −80 °C until use.

5α-Reductase Assay: 5α-Reductase activites were assayed as previously described in the literature.[12] The reaction mixture contained in a final volume of 200 μl: 1 mM DTT, 40 mM of sodium phosphate buffer, 0.1 mM NADPH, 2 nM [1,2,6,7-^{3}H]testosterone, and the rat prostatic enzyme fraction. The amount of the prostatic enzyme fraction was adjusted to set the rate of conversion of testosterone into DHT at around 30% at pH 6.5. The reaction, in duplicate, was started by adding the enzyme fraction, followed by incubation at 37 °C for 60 min, and stopped by mixing with 200—300 μl of ethyl acetate containing cold 500 μg/ml testosterone and 300 μg/ml of DHT as UV markers (245 nm for testosterone, 305 nm for DHT). 50 μl of ethyl acetate was spotted on Kieselgel 60 F254 plates and testosterone and DHT were chromatographed using ethyl acetate : cyclohexane (1 : 1) as the developing solvent. The plate was air dried, sprayed with primuline solution (10 mg/400 ml in acetone : water (4 : 1)), and the testosterone and DHT located under UV light. Androgen containing areas were cut and the strips soaked in 5 ml of aquasol-2 and radioactivities were counted in a scintillation counter.

Effects in Castrated Young Rats: Four-week-old prepubertal male Wistar rats were anesthetized by pentobarbital and castrated. From the incised abdomen vas deferens, testicular artery and vein were fastened and testes were cut out.[13] After 3 d, oral administration of 5 ml/kg of drug solution was started once daily for 5 consecutive days. Drugs were dissolved in sesame oil. 300 μg/kg of TP in sesame oil was subcutaneously injected to the rats at the same time as drug administration. Rats were sacrificed with CO_2 gas about 6 h after the last dosing, and ventral prostates and seminal vesicles were removed and weighed.

References and Notes

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